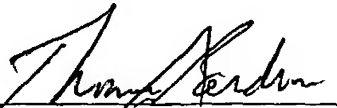


JC10 Rec'd PCT/PTO 15 JAN 2002

<p>(1390 REV. 5-93) US DEPT. OF COMMERCE PATENT & TRADEMARK OFFICE</p> <p align="center">TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371</p>		<p>ATTORNEY'S DOCKET NUMBER 111664</p> <p>U.S. APPLICATION NO. (if known, sec 37 C.F.R.1.5)</p> <p align="center">10/030937</p>
<p>INTERNATIONAL APPLICATION NO. PCT/FR00/02057</p>	<p>INTERNATIONAL FILING DATE July 17, 2000</p>	<p>PRIORITY DATE CLAIMED July 15, 1999</p>
<p>TITLE OF INVENTION USE OF A POLYPEPTIDE FOR DETECTING, PREVENTING OR TREATING A PATHOLOGICAL CONDITION ASSOCIATED WITH A DEGENERATIVE, NEUROLOGICAL OR AUTOIMMUNE DISEASE</p>		
<p>APPLICANT(S) FOR DO/EO/US Dominique ROECKLIN, Hanno KOLBE, Marie-Hélène CHARLES, Carine MALCUS, Lyse SANTORO, Hervé PERRON</p>		
<p>Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:</p> <ol style="list-style-type: none"> 1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371. 2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371. 3. <input checked="" type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1). 4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date. 5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2)) <ol style="list-style-type: none"> a. <input type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau). b. <input checked="" type="checkbox"/> has been transmitted by the International Bureau. c. <input type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US) 6. <input checked="" type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)). 7. <input type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)) <ol style="list-style-type: none"> a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau). b. <input type="checkbox"/> have been transmitted by the International Bureau. c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired. d. <input type="checkbox"/> have not been made and will not be made. 8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)). 9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). 10. <input checked="" type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)). 		
<p>Items 11. to 16. below concern other document(s) or information included:</p>		
<ol style="list-style-type: none"> 11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98. 12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included. 13. <input checked="" type="checkbox"/> A FIRST preliminary amendment. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment. 14. <input type="checkbox"/> A substitute specification. 15. <input type="checkbox"/> Entitlement to small entity status is hereby asserted. 16. <input type="checkbox"/> Other items or information: 		

10/030937
JC13 Rec'd PCT/PTO 15 JAN 2002

U.S. APPLICATION NO. (if known, see 37 C.F.R. 1.5) 10/030937		INTERNATIONAL APPLICATION NO PCT/FR00/02057		ATTORNEY'S DOCKET NUMBER 111664	
17. <input checked="" type="checkbox"/> The following fees are submitted: Basic National fee (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO \$890.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) \$710.00 No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) \$740.00 Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$1,040.00 International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) \$ 100.00 ENTER APPROPRIATE BASIC FEE AMOUNT =				CALCULATIONS	PTO USE ONLY
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
Claims	Number Filed	Number Extra	Rate		
Total Claims	13- 20 =	0	X \$ 18.00	\$	
Independent Claims	1 - 3 =	0	X \$ 84.00	\$	
Multiple dependent claim(s)(if applicable)			+ \$280.00	\$	
TOTAL OF ABOVE CALCULATIONS =				\$890.00	
Reduction by 1/2 for filing by small entity, if applicable.				-	\$
SUBTOTAL =				\$890.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 month from the earliest claimed priority date (37 CFR 1.492(f)).				\$	
TOTAL NATIONAL FEE =				\$890.00	
				Amount to be refunded	\$
				Charged	\$
a. <input checked="" type="checkbox"/> Check No. <u>126891</u> in the amount of <u>\$890.00</u> to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of \$_____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Director is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. <u>15-0461</u> . A duplicate copy of this sheet is enclosed.					
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.					
SEND ALL CORRESPONDENCE TO: OLIFF & BERRIDGE, PLC P.O. Box 19928 Alexandria, Virginia 22320					
				 NAME: William P. Berridge REGISTRATION NUMBER: 30,024	
Date: <u>January 15, 2002</u>				NAME: Thomas J. Pardini REGISTRATION NUMBER: 30,411	

Rec'd PCT/PTO 24 MAY 2002

10/030937

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

BOX: SEQUENCE

Dominique ROECKLIN et al.

Application No.: 10/030,937

Filed: January 15, 2002

Docket No.: 111664

For: USE OF A POLYPEPTIDE FOR DETECTING, PREVENTING OR TREATING A
PATHOLOGICAL CONDITION ASSOCIATED WITH A DEGENERATIVE,
NEUROLOGICAL OR AUTOIMMUNE DISEASE

SUPPLEMENTAL PRELIMINARY AMENDMENT

Director of the U.S. Patent and Trademark Office
Washington, D.C. 20231

Sir:

In reply to the Notification of Missing Requirements mailed March 27, 2002, please
amend the above-identified application as follows:

IN THE SPECIFICATION:

At the end of the application, please replace the current Sequence Listing with the
attached paper and computer-readable Sequence Listing.

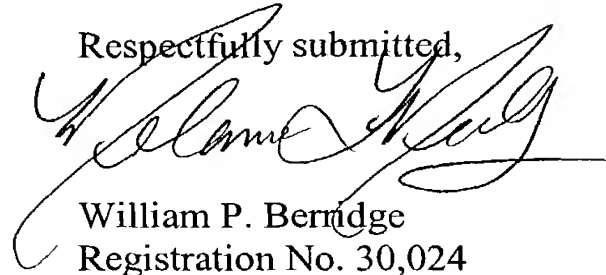
REMARKS

Claims 19-23, 26-30 and 33 are pending.

The attached paper copy and computer-readable copy of the Sequence Listing are
submitted in compliance with 37 C.F.R. §§1.821-1.825. The contents of the paper copy and
the computer-readable copy of the Sequence Listing are the same. No new matter is added.
Support for the information provided in the Sequence Listing can be found in the original
Sequence Listing.

Early and favorable consideration on the merits is respectfully requested.

Respectfully submitted,



William P. Berridge
Registration No. 30,024

Melanie L. Mealy
Registration No. 40,085

WPB:PAC/ja

Attachments:

Sequence Listing (paper and computer-readable copies)

Date: May 24, 2002

OLIFF & BERRIDGE, PLC
P.O. Box 19928
Alexandria, Virginia 22320
Telephone: (703) 836-6400

<p>DEPOSIT ACCOUNT USE AUTHORIZATION Please grant any extension necessary for entry; Charge any fee due to our Deposit Account No. 15-0461</p>
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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Dominique ROECKLIN, Hanno KOLBE,
Marie-Hélène CHARLES, Carine MALCUS,
Lyse SANTORO, Hervé PERRON

Application No.: US National Stage of PCT/FR00/02057

Filed: January 15, 2002

Docket No.: 111664

For: USE OF A POLYPEPTIDE FOR DETECTING, PREVENTING OR TREATING A
PATHOLOGICAL CONDITION ASSOCIATED WITH A DEGENERATIVE,
NEUROLOGICAL OR AUTOIMMUNE DISEASE

PRELIMINARY AMENDMENT

Director of the U.S. Patent and Trademark Office
Washington, D. C. 20231

Sir:

Prior to initial examination, and after entry of the annexes to the IPER, please amend
the above-identified application as follows:

IN THE CLAIMS:

Please cancel claims 1-18, 24-25, 31-32, and 34-59 without prejudice to or disclaimer
of the subject matter contained therein.

Please replace claims 22, 23, 26-29 and 33 as follows:

22. (Amended) The polypeptide as claimed in claim 19, characterized in that it comprises
a protein whose peptide sequence corresponds to SEQ ID No. 9.
23. (Amended) The polypeptide as claimed in claim 19, characterized in that it consists of
a protein whose peptide sequence corresponds to SEQ ID No. 9.

26. (Amended) A method for detecting at least one ligand associated with multiple sclerosis, in a biological sample, characterized in that the biological sample is brought into contact with at least one polypeptide as defined in claim 19, and then the formation of a complex between said polypeptide and the ligand is detected.
27. (Amended) The method as claimed in claim 26, characterized in that the biological sample is in addition brought into contact with at least one polypeptide comprising at least one fragment of a protein chosen from proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1 to SEQ ID No. 8 and SEQ ID No. 10 to SEQ ID No. 29 and the peptide sequences which exhibit at least 70% identity with any one of the peptide sequences SEQ ID No. 1 to SEQ ID No. 8 and SEQ ID No. 10 to SEQ ID No. 29, and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B.
28. (Amended) The method as claimed in claim 26, characterized in that said ligand is an antibody, a receptor, a substrate for enzymatic activity or an enzyme for which said polypeptide is a cofactor.
29. (Amended) A method for detecting at least one polypeptide as defined in claim 19, in a biological sample, characterized in that the biological sample is brought into contact with at least one ligand specific for said polypeptide, and then the formation of a complex between said polypeptide and said ligand is detected.
33. (Amended) A nucleotide fragment, characterized in that it encodes a polypeptide as defined in claim 19.

Please add new claims 60-61 as follows:

- 60. The method as claimed in claim 26, characterized in that the biological sample is urine, cerebrospinal fluid or serum.--
- 61. The method as claimed in claim 29, characterized in that the biological sample is urine, cerebrospinal fluid or serum.--

REMARKS

Claims 19-23, 26-30 and 33 are pending. By this Preliminary Amendment, claims 1-18, 24-25, 31-32 and 34-59 are cancelled and claims 22, 23, 26-29 and 33 are amended to eliminate multiple dependencies and claims 60-61 are added. Prompt and favorable consideration on the merits is respectfully requested.

The attached Appendix includes marked-up copies of each rewritten claim (37 C.F.R. §1.121(c)(1)(ii)).

Respectfully submitted,



William P. Berridge
Registration No. 30,024

Thomas J. Pardini
Registration No. 30,411

WPB:TJP/zmc

Attached: APPENDIX

Date: January 15, 2002

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Alexandria, Virginia 22320
Telephone: (703) 836-6400

DEPOSIT ACCOUNT USE AUTHORIZATION Please grant any extension necessary for entry; Charge any fee due to our Deposit Account No. 15-0461
--

APPENDIX

Changes to Claims:

Claims 1-18, 24-25, 31-32, and 34-59 are canceled.

Claims 60-61 are added.

The following are marked-up versions of the amended claims:

22. (Amended) The polypeptide as claimed in claim 19~~one of claims 19 to 21~~, characterized in that it comprises a protein whose peptide sequence corresponds to SEQ ID No. 9.
23. (Amended) The polypeptide as claimed in claim 19~~one of claims 19 to 21~~, characterized in that it consists of a protein whose peptide sequence corresponds to SEQ ID No. 9.
26. (Amended) A method for detecting at least one ligand associated with multiple sclerosis, in a biological sample, characterized in that the biological sample is brought into contact with at least one polypeptide as defined in claim 19~~any one of claims 19 to 23~~, and then the formation of a complex between said polypeptide and the ligand is detected.
27. (Amended) The method as claimed in claim 26, characterized in that the biological sample is in addition brought into contact with at least one polypeptide ~~as defined in any one of claims 1 to 5~~ comprising at least one fragment of a protein chosen from proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1 to SEQ ID No. 8 and SEQ ID No. 10 to SEQ ID No. 29 and the peptide sequences which exhibit at least 70% identity with any one of the peptide sequences SEQ ID No. 1 to SEQ ID No. 8 and SEQ ID No. 10 to SEQ ID No. 29, and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from

Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B.

28. (Amended) The method as claimed in claim 26-~~or 27~~, characterized in that said ligand is an antibody, a receptor, a substrate for enzymatic activity or an enzyme for which said polypeptide is a cofactor.
29. (Amended) A method for detecting at least one polypeptide as defined in claim 19~~any one of claims 19 to 23~~, in a biological sample, characterized in that the biological sample is brought into contact with at least one ligand specific for said polypeptide, and then the formation of a complex between said polypeptide and said ligand is detected.
33. (Amended) A nucleotide fragment, characterized in that it encodes a polypeptide as defined in claim 19~~any one of claims 19 to 23~~.

WO 01/05422

PCT/FR00/02057

18/1/01

**USE OF A POLYPEPTIDE FOR DETECTING, PREVENTING
OR TREATING A PATHOLOGICAL CONDITION ASSOCIATED
WITH A DEGENERATIVE, NEUROLOGICAL OR AUTOIMMUNE DISEASE**

5 The present invention relates in particular to the use
of at least one polypeptide to obtain a diagnostic,
prognostic, prophylactic or therapeutic composition for
for detecting, preventing or treating a pathological
condition associated with a degenerative and/or
10 autoimmune and/or neurological disease.

According to the invention, the expression degenerative
disease is understood to mean a disease in which a
process of cell death or of cell destruction is
15 associated with physiological and/or clinical
disorders. Alzheimer's disease, amyotrophic lateral
sclerosis and Parkinson's disease are classified
amongst neurodegenerative diseases. The expression
autoimmune disease is understood to mean a
20 hyperactivity of the immune system toward one or more
autoantigens. Multiple sclerosis (MS), rheumatoid
arthritis (RA) and lupus erythematosus are classified
among autoimmune diseases.

25 Multiple sclerosis is a chronic disease of the central
nervous system in humans which progresses through a
succession of phases of remission and of flare-up or in
a regular progression and whose anatomicopathological
characteristic consists in the formation of well
30 delimited demyelination zones in the white substance of
the brain and of the spinal cord.

At the histological level, these zones exhibit, at the
early stage of the lesional process, a degradation of
35 the periaxonal myelin associated with an impairment of
the glial cells responsible for this demyelination.
Inflammatory macrophage activation causing the
microglial cells (resident tissue macrophages of the

- 2 -

central nervous system), as well as, probably, macrophages from infiltrated blood monocytes, is associated with this demyelination process and contributes to the destruction of the myelinated
5 sheets. At the center of the demyelinated zone, there is a relative depletion of glial cells whereas a proliferation of astrocytes develops at the periphery and can invade the demyelinated plaque in order to generate a fibrous or gliotic plaque. These sclerotic
10 structures are responsible for the name given to the disease.

Another characteristic of these plaques is their almost systematic association with a vascular element around
15 which they develop.

At the histological level, a frequent alteration of the blood-brain barrier (BBB) consisting of capillary endothelium is observed. One of the key elements in
20 maintaining the BBB consists of the underlying presence of cytoplasmic extensions of the astrocytes, called astrocytic feet. Possibly, the astrocytic feet induce the formation or allow the maintenance of tight joining structures which ensure the cohesion of the capillary
25 endothelial barrier concretizing the BBB. However, various pathological models report the alteration of the BBB and a depletion of the astrocytic feet.

Moreover, in the lesional process in MS, the alteration
30 of the BBB contributes toward amplifying the associated inflammatory response by the influx of lymphoid cells from the bloodstream. The contribution of the inflammation associated with the immune cells is important in MS and participates in the lesional
35 process.

The etiology of MS is the source of a current debate because the disease could have various origins. Hypotheses have been emitted on a bacterial and/or

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viral origin. Moreover, as described in patent application WO 95/21859, H. Perron et al. have been led to investigate one or more effector agents for the pathogenic process resulting in the typical formation of demyelination plaques and in astrocytic gliosis. In the context of this study, they demonstrated the presence, in the cerebrospinal fluid (CSF) and the serum of MS patients, of at least one factor which exhibits a toxic activity toward human or animal astrocyte and oligodendrocyte cells. This toxic activity is characterized by a cytomorphological disorganization of the network of intermediate filaments and/or a degradation of the proteins of said filaments and/or a cell death by apoptosis of the glial cells. They established a significant correlation between the *in vitro* detection of this toxic activity in samples of CSF and of serum of MS patients and multiple sclerosis by a quantitative colorimetric assay with methyltetrazolium bromide (MTT) of the live cells, as described in patent application WO 95/21859. Moreover, C. Malcus-Vocanson et al. have shown that urine is a very favorable biological fluid for the detection of the activity of this toxic factor and developed a method using flow cytometry to detect and/or quantify the adherent glial cells which are dead through apoptosis. All the information relating to this method is described in patent application WO 98/11439, whose content is incorporated by way of reference.

Trials were carried out starting with a protein fraction of CSF and of urine from MS patients in order to try to identify this toxic factor. The protein content of each fraction was separated on a 12% SDS-PAGE gel and observed after silver staining of the gel. Among the proteins observed, a protein fraction centered over an apparent molecular weight of about 21 kD was found not predominantly associated with the toxic activity detected *in vitro* and a fraction centered over an apparent molecular weight of about

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17 kD was found predominantly associated with the toxic activity.

Injection of the fraction from the SCF of MS patients
5 into the brain of Lewis rats and postmortem
histological observation of brain sections of the rats
made it possible to observe, three months after the
injection, an apoptosis of the astrocytic population
and the formation of demyelination plaques. All the
10 information is contained in patent application
WO 97/33466, whose content is incorporated by way of
reference. These observations are in accordance with
those which have been made on the brain sections of
patients suffering from MS, after biopsy (N. Benjelloun
15 et al. Cell. Mol. Biol., 1998, 44(4), 579-583).

The present inventors have now identified and analyzed
the proteins associated with this toxic activity toward
glial cells in biological samples from MS patients, in
20 particular in urine, cerebrospinal fluid and serum.

After purification of the proteins and separation on
SDS-TRICINE gel, the inventors have demonstrated the
presence of four bands of interest having different
25 apparent molecular weights, of 8, 14, 18 and 20 kD
respectively, corresponding to at least five different
protein families. The proteins of these families were
then analyzed by mass spectrometry and/or sequencing
and a search for homology in data banks (NCBI
30 <http://ww.ncbi.nlm.nih.gov>, Basic Blast Search, Protein
Blastp, the protein sequences are entered in a FASTA
format into the nr database, the algorithm used is
Matrix BLOSUM62, the identity called "Identities"
corresponds to the number of identical amino acids,
35 given as a percentage, and the positivity "Positives"
corresponds to the amino acids exhibiting biological
equivalence according to the abovementioned parameters
of the software, given as a percentage). These proteins
belong to the protein families of Perlecan, of the

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precursor of the retinol-binding plasma protein, of the precursor of the ganglioside GM2 activator, of calgranulin and of saposin B. More precisely, the proteins are (i) for the 20 kD band, the C-terminal
5 fragment of Perlecan which starts at amino acid 3464 and ends at amino acid 3707 (Murdoch AD et al. J Biol Chem, 1992, April 25; 267 (12):8544-47), and designated by a reference in the sequence identifier SEQ ID No. 2 (the full-length Perlecan protein being designated by a
10 reference in SEQ ID No. 1), (ii) for the 20 kD band, the precursor of the retinol-binding plasma protein (Monaco HL et al., Science, 1995, 268 (5213):1039-1041) whose sequence is given in SEQ ID No. 4 (iii) for the 18 kD band, the precursor of the ganglioside GM2
15 activator (Furst W et al., Euro J Biochem, 1990, Sep 24; 193(3):709-14) identified in SEQ ID No. 8, (iv) for the 14 kD band, calgranulin B (Lagasse. E et al., Mol Cell Biol, 1988, Jun;8(6):2402-10) identified in SEQ ID No. 17 and (v) for the 8 kD band, saposin B
20 (Kleinschmidt T et al., Biol Chem Hoppe Seyler, 1988, Dec;369(12):1361-5) represented in SEQ ID No. 24. They have also demonstrated the presence of variant sequences to said reference sequences, in particular for the 18 kD band a variant sequence of the precursor
25 of the ganglioside GM2 activator designated by the reference SEQ ID No. 9. These variant protein sequences are the product of mutations at the level of the genes encoding said proteins or are the result of splicing phenomena. It should be noted, for example, that
30 calprotectin is a variant of calgranulin B.

The C-terminal fragment of the Perlecan protein (SEQ ID No. 2) is encoded, for example, by the DNA nucleotide sequence SEQ ID No. 69, taking into account the genetic
35 code. The precursor protein for the retinol-binding plasma protein (SEQ ID No. 4) is encoded, for example, by the DNA nucleotide sequence SEQ ID No. 70, taking into account the genetic code. The GM2 activator protein (SEQ ID No. 8) is encoded, for example, by the

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DNA nucleotide sequence SEQ ID No. 31, taking into account the genetic code. The peptides FSWDNCFEGK DPAVIR and YSLPKSEFAV PDLELP derived from the GM2 activator mutated polypeptide (SEQ ID No. 9) are
5 encoded by the DNA nucleotide sequences SEQ ID No. 66 and SEQ ID No. 67, respectively, taking into account the genetic code. The calgranulin B protein (SEQ ID No. 17) is encoded, for example, by the DNA nucleotide sequence SEQ ID No. 42, taking into account the genetic
10 code. The saposin B protein (SEQ ID No. 24) is encoded, for example, by the DNA nucleotide sequence SEQ ID No. 53, taking into account the genetic code.

The expression protein family is understood to mean all
15 the proteins encoded from the same DNA gene and which result from a differential multiple splicing of the gene and/or of a different reading frame. The DNA gene is transcribed with alternative splicing phenomena, leading to the translation of different primary
20 sequences of proteins. All these proteins belong to the same protein family. The term "protein family" also includes proteins which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with a reference protein sequence of
25 the family.

The expression multiple splicing is understood to mean a splicing occurring at least once in the nucleotide region of interest.

30

For example, the expression precursor protein family for the retinol-binding plasma protein designates the protein family comprising at least the proteins or fragments of proteins having the sequence SEQ ID No. 4,
35 SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, and the proteins encoded by the corresponding gene according to different reading frames.

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For example, the expression GM2 activator protein family designates the protein family comprising at least the proteins or fragments of proteins having the sequence SEQ ID No. 8, SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14,, SEQ ID No. 15, SEQ ID No. 16, and the proteins encoded by the corresponding gene according to different reading frames, which result from a differential multiple splicing of the gene and/or of a different reading frame.

For example, the expression calgranulin B protein family designates the protein family comprising at least the proteins or fragments of proteins having the sequence SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22, SEQ ID No. 23, and the proteins encoded by the corresponding gene according to different reading frames, which result from a differential multiple splicing of the gene and/or of a different reading frame. The proteins MRP14 (SEQ ID No. 17) and MRP8 (SEQ ID No. 18) have a different protein sequence while being encoded by the same gene; they belong to the same protein family.

For example, the expression saposin B protein family designates the protein family comprising at least the proteins or fragments of proteins having the sequence SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28, SEQ ID No. 29, and the proteins encoded by the corresponding gene according to different reading frames, which result from a differential multiple splicing of the gene and/or of a different reading frame.

The expression nucleic acid family encoding a protein is understood to mean all the cDNA and/or RNA nucleic sequences transcribed from the same DNA gene and which result from a differential multiple splicing. The DNA gene is transcribed with differential splicing

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phenomena and leads to the synthesis of different nucleic acids (cDNA, RNA) of different sequences. All these cDNA and mRNA sequences are considered to belong to the same nucleic acid family.

5

For example, the expression nucleic acid family encoding the precursor protein family for the retinol-binding plasma protein designates the nucleic acid family comprising at least the nucleic acids or fragments having the sequence SEQ ID No. 30.

10

For example, the expression nucleic acid family encoding the GM2 activator protein family designates the nucleic acid family comprising at least the nucleic acids or fragments having the sequences SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 35, SEQ ID No. 36, SEQ ID No. 37, SEQ ID No. 38, SEQ ID No. 39, SEQ ID No. 40, SEQ ID No. 41 which result from a differential multiple splicing of the gene and/or of a different reading frame.

15

20

For example, the expression nucleic acid family encoding the calgranulin B protein family designates the nucleic acid family comprising at least the nucleic acids or fragments having the sequences SEQ ID No. 42, SEQ ID No. 43, SEQ ID No. 44, SEQ ID No. 45, SEQ ID No. 46, SEQ ID No. 47, SEQ ID No. 48, SEQ ID No. 49, SEQ ID No. 50, SEQ ID No. 51, SEQ ID No. 52 which result from a differential multiple splicing of the gene and/or of a different reading frame.

25

30

For example, the expression nucleic acid family encoding the saposin B protein family designates the nucleic acid family comprising at least the nucleic acids or fragments having the sequences SEQ ID No. 53, SEQ ID No. 54, SEQ ID No. 55 which result from a differential multiple splicing of the gene and/or of a different reading frame.

35

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The expression "splicing" is understood to mean a mechanism of excision of the introns and of joining of the exons during the maturation of the transcripts and the expression "differential splicing" is understood to mean the existence of several schemes for splicing of a primary transcript resulting in the formation of different messenger RNAs and capable of leading to the synthesis of several different proteins (Kaplan and Delpech, Biologie Moléculaire et Médecine, 1993, 2nd edition, Médecine et Sciences, Flammarion, pages 73-77). This phenomenon is widely described in the scientific literature. By way of example, there may be mentioned the model of the genes which encode the heavy and light immunoglobulin chains, the model of the gene for dystrophin, the model of the gene for alpha-amylase, the gene for myelin, and the like.

It is known that the eukaryotic genes in particular comprise regions (exons) which encode fragments of the protein encoded by said gene and other regions (introns) which do not have a protein equivalent. This is due to the fact that the genes are first transcribed to a "primary" RNA which is then cut by splicing enzymes at the level of specific nucleotide sites (splicing sites). These enzymes then join the regions encoding the protein, thus reconstituting a "secondary" RNA from which the intron regions have been removed. Moreover, depending on the cellular phenotypes (and therefore the tissues or the differentiation), these enzymes are not all expressed, and thus the same RNA may be differently spliced in the cells of the same individual, thus generating proteins with differences in sequence. However, these phenomena may also be applied to nucleotide regions which are completely coding (exons), but which, according to different possible splicings, will generate several different proteins from the same nucleotide region by the phenomenon of differential splicing between the different protein products.

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Furthermore, it is known that nucleotide regions may have several reading frames according to the three potential frames of the genetic code. Thus, the presence of several initiation codons for translation in several reading frames and/or a splicing of primary RNA joining nucleotide sequences present in different reading frames on the DNA, allows the same DNA region to generate protein products with no mutual relationship from the point of view of the peptide sequence.

Finally, the genetic polymorphism existing between individuals of the same species and/or individual mutations can create or eliminate splicing sites from a given DNA region, and thus modify the sequence and the structure of the protein product(s) normally produced by this region.

Thus, the combination of these different phenomena can allow the same nucleotide sequence corresponding to a DNA segment, identified as determining a genetic region of interest in a given study, to comprise the information which is necessary and sufficient to define a whole family of RNA spliced according to different and alternative schemes, in various reading frames and, thereby obviously, proteins and polypeptides having "mosaic" sequences according to one reading frame or even according to the three potential frames and mutations possibly linked to genetic polymorphism.

An example of this phenomenon may be represented by the nucleotide region of the HIV-1 retrovirus *env* gene. Indeed, several different proteins are encoded by segments of the same sequence: for example, the envelope glycoprotein, and the regulatory proteins TAT, REV, NEF, VIF.

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It is also known that proteins may result from the assembly of identical subunits (homodimers, homomultimers) or different subunits (heterodimers, heteromultimers). Thus, the various protein products
5 encoded by the same DNA region may also assemble with each other to constitute multimeric complex protein entities. This phenomenon is in addition to the preceding ones and, when a protein is identified by a peptide fragment, it is possible to logically identify
10 all the other constituent elements of this complex protein and the spliced RNA and DNA segments encoding them, as well as all the members of the family of protein products and their assemblies. Another example is provided by the human DNA region encoding the family
15 of MRP14, calgranulin B, MRP8, calprotectin and psoriasin proteins, and the like.

Accordingly, the subject of the present invention is the use of at least one polypeptide comprising at least
20 one fragment of a protein to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological condition associated with a degenerative and/or autoimmune disease, said protein being chosen
25 from proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15,
30 SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28 and SEQ ID No. 29 and the peptide sequences which exhibit at least 70% identity,
35 preferably at least 80% identity and advantageously at least 98% identity with any of the abovementioned peptide sequences, and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor

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of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B. In specific embodiments, at least two abovementioned polypeptides are used in combination in order to obtain
5 a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological condition associated with a degenerative and/or autoimmune disease.

10 The invention also relates to the use of at least one polypeptide comprising at least one fragment of a protein to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting,
15 condition associated with a degenerative and/or autoimmune disease, said protein being chosen from the proteins whose peptide sequence in the native state corresponds to SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 8, SEQ ID No. 17 and SEQ ID No. 24 and the peptide
20 sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the abovementioned peptide sequences. Advantageously, the five polypeptides which correspond to the above definition
25 are used in combination.

Preferably, the peptide sequence of said polypeptide comprises, or consists of, a sequence chosen from any one of SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 8, SEQ ID
30 No. 17 and SEQ ID No. 24.

The invention also relates to the use of at least one fragment of one of the abovementioned polypeptides for the preparation of an immunogenic peptide, said peptide
35 comprising all or part of at least one of the sequences designated by the references SEQ ID Nos. 58 to 65 and being used for the production of monoclonal antibodies.

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The subject of the invention is also the use of at least one nucleotide fragment to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological condition associated with a degenerative and/or autoimmune disease, according to which said nucleotide fragment is chosen from fragments which encode at least one fragment of a protein, said protein being chosen from proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28 and SEQ ID No. 29 and the peptide sequences which exhibit at least 70% identity, preferably at least 80% and advantageously at least 98% identity with any one of the above peptide sequences, and the fragments complementary to said fragments, and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B. It is within the capability of persons skilled in the art to determine the nucleic sequences of the nucleotide fragments from the peptide sequences and the genetic code, this forming part of their general knowledge.

Preferably, said nucleotide fragment encodes a protein which, in the native state, consists of a sequence chosen from any one of the sequences SEQ ID Nos. 1 to 8 and SEQ ID Nos. 10 to 29 cited above, and among the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma

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protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B.

Another subject of the invention is the use of at least
5 one nucleotide fragment to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological condition associated with a degenerative and/or neurological and/or autoimmune disease according
10 to which said fragment is a fragment of a nucleic sequence chosen from any one of SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 35, SEQ ID No. 36, SEQ ID No. 37, SEQ ID No. 38, SEQ ID No. 39, SEQ ID No. 40, SEQ ID No. 41, SEQ ID
15 No. 42, SEQ ID No. 43, SEQ ID No. 44, SEQ ID No. 45, SEQ ID No. 46 and SEQ ID No. 47, SEQ ID No. 48, SEQ ID No. 49 and SEQ ID No. 50, SEQ ID No. 51, SEQ ID No. 52, SEQ ID No. 53, SEQ ID No. 54, SEQ ID No. 55, SEQ ID No. 56, SEQ ID No. 57, SEQ ID No. 67, SEQ ID No. 66, SEQ ID
20 No. 69, SEQ ID No. 70 and SEQ ID No. 71, and their complementary sequences.

The invention also relates to the use of a ligand specific for a polypeptide or for a nucleotide fragment
25 as defined above to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological condition associated with a degenerative and/or autoimmune disease.

30

The expression ligand is understood to mean any molecule capable of combining with a polypeptide, such as a monoclonal antibody, a polyclonal antibody, a receptor, a substrate with enzymatic activity, or an
35 enzyme for which said polypeptide is a cofactor. The production of polyclonal or monoclonal antibodies forms part of the general knowledge of persons skilled in the art. There may be mentioned, by way of reference, Köhler G. and Milstein C. (1975): Continuous culture of

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fused cells secreting antibody of predefined specificity, Nature 256:495-497 and Galfre G. et al. (1977) Nature, 266:522-550 for the production of monoclonal antibodies and Roda A., Bolelli G.F.:
 5 Production of high-titer antibody to bile acids, Journal of Steroid Biochemistry, Vol. 13, pp. 449-454 (1980) for the production of polyclonal antibodies.

The expression ligand is also understood to mean any
 10 molecule capable of combining with a nucleotide fragment, such as a partially or completely complementary nucleotide fragment, a complementary polynucleotide, or an anti-nucleic acid antibody. The production of nucleotide fragments or of
 15 polynucleotides forms part of the general knowledge of persons skilled in the art. There may be mentioned in particular the use of restriction enzymes, and chemical synthesis on an automated synthesizer, for example on synthesizers marketed by the company Applied Biosystem.
 20 Moreover, techniques for the production of anti-nucleic acid antibodies are known. There may be mentioned, by way of examples, Philippe Cros et al., Nucleic Acides Researc, 1994, Vol. 22, No. 15, 2951-2957; Anderson, W.F. et al. (1988) Bioessays, 8(2), 69-74; Lee, J.S. et
 25 al. (1984) FEBS Lett., 168, 303-306; Malfoy, B. et al. (1982) Biochemistry, 21(22), 5463-5467; Stollar, B.D. et al., J.J. (eds) Methods in Enzymology, Academic Press, pp. 70-85; Traincard, F. et al. (1989) J. Immunol. Meth., 123, 83-91 and Traincard, F. et al.
 30 (1989) Mol. Cell. Probes, 3, 27-38).

The subject of the invention is also a method for detecting at least one protein associated with a degenerative and/or autoimmune disease in a biological
 35 sample in which the biological sample is brought into contact with at least one ligand specific for at least one polypeptide, said polypeptide comprising at least one fragment of a protein and said protein being chosen from the proteins whose peptide sequence in the native

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state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28 and SEQ ID No. 29 and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to SEQ ID No. 8 and SEQ ID No. 10 to 29, and the peptide sequences or fragments of said sequences belonging to the same family of proteins. chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B, and then the formation of a complex between said polypeptide and said ligand is detected. Said ligand is advantageously a monoclonal antibody, a polyclonal antibody, a receptor, a substrate with enzymatic activity or an enzyme for which said polypeptide is a cofactor.

Likewise, the invention relates to a method for detecting at least one ligand associated with a degenerative and/or autoimmune disease, in a biological sample, characterized in that the biological sample is brought into contact with at least one polypeptide comprising at least one fragment of a protein, said protein being chosen from the proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28 and SEQ ID No. 29 and the peptide sequences which exhibit

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at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to SEQ ID No. 8 and SEQ ID Nos. 10 to SEQ ID No. 29, and the peptide
5 sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B, and then the formation of a complex
10 between said polypeptide and said ligand is detected. The ligand is any molecule which satisfies the conditions previously described.

Preferably, in the methods described above, the
15 sequence of the polypeptide comprises or consists of a peptide sequence chosen from any one of SEQ ID No. 1 to 8 and SEQ ID No. 10 to 29 above and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan,
20 the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B.

The invention also relates to a novel polypeptide which
25 comprises at least one fragment of a protein whose peptide sequence corresponds to SEQ ID No. 9, said fragment exhibiting at least one mutation, in particular at least two mutations, in relation to the reference sequence SEQ ID No. 8. The polypeptide is
30 advantageously chosen from the polypeptides which comprise the amino acid sequence FSWDNCFEGKDPVIR, designated by the reference SEQ ID No. 68, and the amino acid sequence YSLPKSEFAVPDLELP, designated by the reference SEQ ID No. 72.

35

In particular, said polypeptide comprises or consists of SEQ ID No. 9. This polypeptide is used to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing

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or treating a pathological condition associated with a degenerative and/or autoimmune disease, alone or as a mixture with at least one polypeptide as defined above.

5 One of the subjects of the invention is also a nucleotide fragment which encodes the fragment of the protein whose peptide sequence corresponds to SEQ ID No. 9, said fragment of said protein exhibiting at least one mutation, in particular two mutations
10 relative to the reference sequence SEQ ID No. 8. Said nucleotide fragment in particular comprises or consists of a fragment which encodes SEQ ID No. 9. This fragment is used to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting,
15 preventing or treating a pathological condition associated with a degenerative and/or autoimmune disease, alone or as a mixture with at least one nucleotide fragment as defined above.

20 The subject of the invention is also a method for detecting at least one ligand associated with a degenerative and/or autoimmune disease, in a biological sample, according to which the biological sample is brought into contact with at least the polypeptide
25 which comprises or consists of SEQ ID No. 9 or a mixture of polypeptides comprising this polypeptide and at least one polypeptide as described above, and then the formation of a complex or of complexes between the polypeptide(s) and the corresponding ligand(s) is
30 detected; it is to be understood that the expression ligand is understood to mean a molecule which satisfies the abovementioned conditions.

The invention also relates to a method for detecting at
35 least the reference polypeptide SEQ ID No. 9 or a fragment of said polypeptide, this fragment comprising at least one and preferably two mutations in relation to the reference sequence SEQ ID No. 8, in a biological sample according to which the biological sample is

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brought into contact with at least one ligand specific for said polypeptide, and then the formation of a complex between said polypeptide and said ligand is detected. The definition of ligand corresponds to that defined above. It may be, inter alia, a monolonal antibody, a polyclonal antibody, a substrate with enzymatic activity or an enzyme for which said polypeptide is a cofactor, or a receptor.

10 It is also possible to bring the biological sample into contact with a ligand specific for the reference polypeptide SEQ ID No. 9 and at least one ligand specific for at least one other polypeptide as defined above, and then the formation of complexes between said
15 polypeptides and said ligands specific for said polypeptides is detected; it being understood that the expression ligand is understood to mean a molecule which satisfies the conditions described above.

20 Another subject of the invention is a nucleotide fragment encoding all or part of the polypeptide SEQ ID No. 9, and its use to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological
25 condition associated with a degenerative and/or autoimmune disease, optionally in combination with at least one nucleotide fragment as defined above, and the fragments complementary to said fragments.

30 The expression polypeptide fragment is understood to mean at least all or part of the peptide sequence of a protein, in particular a polypeptide fragment which comprises between about 5 and 15 amino acids and more precisely between about 5 and 10 amino acids and 6 and
35 15 amino acids. The expression nucleotide fragment is understood to mean at least all or part of a nucleotide sequence, it being understood that the expression nucleotide sequence covers DNA and RNA sequences.

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In particular, the expression polypeptide or nucleotide fragment is understood to mean either fragments associated with the same molecular unit, or fragments in a molecular complex comprising several homologous or
 5 heterologous subunits obtained naturally or artificially, in particular by differential multiple splicing or by selective synthesis.

The invention also relates to a method for detecting at
 10 least one polypeptide as defined above, according to which a sample of a biological fluid is collected from a patient having a pathological condition associated with a degenerative and/or neurological and/or autoimmune disease and, optionally after purification
 15 of said sample of biological fluid, the mass profile obtained from the biological fluid is analyzed by mass spectrometry and compared with a reference mass profile.

20 The present invention also relates to the use of at least one polypeptide of the invention to define therapeutically effective agents, and the use of these agents to prevent and/or treat an autoimmune and/or neurological and/or degenerative disease, and in
 25 particular multiple sclerosis.

Thus, other subjects of the invention are the following:

30 - Use of at least one polypeptide comprising at least one fragment of a protein to test the efficacy of a therapeutic agent, said protein being chosen from the proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No.
 35 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8, SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID

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No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25,
SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28 and SEQ ID
No. 29, the peptide sequences which exhibit at least
70% identity, preferably at least 80% identity and
5 advantageously at least 98 identity with any one of the
peptide sequences SEQ ID No. 1 to 29, and the peptide
sequences or the fragments of said sequences belonging
to the same family of proteins chosen from Perlecan,
the precursor of the retinol-binding plasma protein,
10 precursor of the ganglioside GM2 activator, calgranulin
B and saposin B;

- Use of at least one polypeptide comprising at
least one fragment of a protein to define a biological
15 material for the preparation of a pharmaceutical
composition for treating a degenerative and/or
neurological and/or autoimmune disease, such as
multiple sclerosis, said protein being chosen from the
proteins whose peptide sequence in the native state
20 corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No.
3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No.
7, SEQ ID No. 8, SEQ ID No. 9, SEQ ID No. 10, SEQ ID
No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14,
SEQ ID No. 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID No.
25 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID
No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25,
SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28 and SEQ ID
No. 29, the peptide sequences which exhibit at least
70% identity, preferably at least 80% identity and
30 advantageously at least 98 identity with any one of the
peptide sequences SEQ ID No. 1 to 29, and the peptide
sequences or the fragments of said sequences belonging
to the same family of proteins chosen from Perlecan,
the precursor of the retinol-binding plasma protein,
35 precursor of the ganglioside GM2 activator, calgranulin
and saposin;

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According to an advantageous variant of one of the preceding uses, the polypeptide is chosen from SEQ ID No. 2, 4, 8, 9, 17, 24;

5 - Use of at least one nucleotide fragment to test the efficacy of a therapeutic agent for a pathological condition associated with a degenerative and/or neurological and/or autoimmune disease, according to which said nucleotide fragment is chosen from the
10 fragments which encode at least one fragment of a protein, said protein being chosen from the proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No.
15 8, SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26,
20 SEQ ID No. 27, SEQ ID No. 28 and SEQ ID No. 29, the peptide sequences which exhibit at least 70% identity, preferably at least 80% and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, and the fragments complementary to said
25 fragments and the fragments which encode the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin
30 B and saposin B.

- Use, to test the efficacy of a therapeutic agent for a pathological condition associated with a degenerative and/or neurological and/or autoimmune
35 disease, of recombinant proteins and/or proteins encoded by all or part of the nucleotide fragments defined in the above paragraph;

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- Use of at least one nucleotide fragment for the preparation of a pharmaceutical composition for treating a degenerative and/or neurological and/or autoimmune disease, such as multiple sclerosis, according to which said nucleotide fragment is chosen from fragments which encode at least one fragment of a protein, said protein being chosen from the proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8, SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28 and SEQ ID No. 29, the peptide sequences which exhibit at least 70% identity, preferably at least 80% and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, and the fragments complementary to said fragments and the fragments which encode the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B;

- Use, for the preparation of a pharmaceutical composition for treating a degenerative and/or neurological and/or autoimmune disease, such as multiple sclerosis, of recombinant proteins and/or proteins encoded by all or part of the nucleotide fragments defined in the preceding paragraph.

Advantageously, said nucleotide fragment used encodes said protein.

Preferably, the peptide sequence of said protein in the native state consists of a sequence chosen from any one

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of SEQ ID No. 1 to 29, the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29, and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B. The polypeptides are preferably chosen from SEQ ID No. 2, 4, 8, 9, 17, 24.

- Use of at least one nucleotide fragment to test the efficacy of a therapeutic agent for a pathological condition associated with a degenerative and/or neurological and/or autoimmune disease, according to which said fragment is a fragment of a nucleic sequence chosen from any one of SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 35, SEQ ID No. 36, SEQ ID No. 37, SEQ ID No. 38, SEQ ID No. 39, SEQ ID No. 40, SEQ ID No. 41, SEQ ID No. 42, SEQ ID No. 43, SEQ ID No. 44, SEQ ID No. 45, SEQ ID No. 46 and SEQ ID No. 47, SEQ ID No. 48, SEQ ID No. 49 and SEQ ID No. 50, SEQ ID No. 51, SEQ ID No. 52, SEQ ID No. 53, SEQ ID No. 54, SEQ ID No. 55, SEQ ID No. 56, SEQ ID No. 57, SEQ ID No. 66, SEQ ID No. 67, SEQ ID No. 69, SEQ ID No. 70, SEQ ID No. 71, and their complementary sequences.

- Use of at least one nucleotide fragment for the preparation of a pharmaceutical composition for treating a degenerative and/or neurological and/or autoimmune disease, such as multiple sclerosis, according to which said fragment is a fragment of a nucleic sequence chosen from any one of SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 35, SEQ ID No. 36, SEQ ID No. 37, SEQ ID No. 38, SEQ ID No. 39, SEQ ID No. 40, SEQ ID No. 41, SEQ ID No. 42, SEQ ID No. 43, SEQ ID No. 44, SEQ ID No.

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45, SEQ ID No. 46 and SEQ ID No. 47, SEQ ID No. 48, SEQ ID No. 49 and SEQ ID No. 50, SEQ ID No. 51, SEQ ID No. 52, SEQ ID No. 53, SEQ ID No. 54, SEQ ID No. 55, SEQ ID No. 56, SEQ ID No. 57, SEQ ID No. 66, SEQ ID No. 67, 5 SEQ ID No. 68, SEQ ID No. 69, SEQ ID No. 70, SEQ ID No. 71, and their complementary sequences.

The nucleic sequence is preferably chosen from SEQ ID No. 30, 31, 42, 53.

10

- Use of lycorine for the preparation of a composition for preventing and/or treating a degenerative and/or neurological and/or autoimmune disease.

15

The expression therapeutic efficacy is understood to mean the clinical and biological benefit acquired after administration of a therapeutic agent for the purpose of improving or even curing the disease. This benefit 20 is manifested, inter alia, by a reduction in the clinical and biological signs, and in the pathological effects of the disease after clinical analysis by the doctor and/or biological analyses, such as magnetic resonance imaging, analysis of the oligoclonal bands in 25 the cerebrospinal fluid, analysis of evoked potentials and the test for detection of gliotoxicity called bioassay, whose principle is described in patent application WO 98/11439 cited above. This reduction in the clinical signs and pathological effects should 30 result in a benefit for the patient (Schwartz and Lazar, 1995, Elements de statistique médicale et biologique, eds Flammarion; Lazar and Schwartz, 1995, Eléments de statistique médicale et biologique, eds Flammarion). The disease studied is preferably multiple 35 sclerosis.

The expression composition for prophylactic and/or therapeutic use is understood to mean any composition which comprises an effective therapeutic agent. These

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therapeutic agents are capable (i) of qualitatively and/or quantitatively influencing the biological activity and/or the function of the proteins of interest identified in the present invention, preferably the gliotoxic activity and/or (ii) modulating and/or inhibiting the expression of these proteins and/or (iii) reducing the concentration of these proteins in an extracellular and/or intracellular compartment, and/or substituting a nonpathogenic form for a pathogenic, for example mutated, form of one of these proteins and/or modulating their attachment to at least one of their ligands; said ligand being a molecule which satisfies the criteria described above. Various therapeutic agents are produced based on the conventional approaches widely described in the literature. The various groups of therapeutic agents defined from the proteins of interest identified in this present invention are described below. Their prophylactic and/or therapeutic efficacy or activity is evaluated *in vitro* and/or *in vivo*.

Evaluation of the efficacy of a therapeutic agent *in vitro*: urine samples from healthy individuals and from patients suffering from multiple sclerosis, preferably in the active phase, are tested for their gliotoxic activity *in vitro* based on the bioassay protocol described in patent application WO 98/11439, cited above. The experiment is carried out in parallel by adding or otherwise, to the urine samples tested, the therapeutic agent whose efficacy is to be tested. Assays are carried out at various concentrations of this agent, and after various incubation times with the sample, at a temperature of about 37°C or at room temperature, for each concentration of agent tested, before carrying out the bioassay test. The gliotoxic activity is determined for each crude or purified sample of control and patient's urine in the presence or in the absence of tested therapeutic agent. A prophylactic and/or therapeutic agent for multiple

sclerosis is an agent which allows a reduction or an inhibition of the gliotoxic activity in a biological fluid from the patients, in particular in the urine. This reduction or inhibition is evaluated relative to
 5 the gliotoxic activity detected in the biological fluid of MS patients in the absence of the test agent which defines the upper limit and relative to the gliotoxic activity detected in the urine of a healthy individual which determines the lower limit (Schwartz and Lazar,
 10 1995, Elements de statistique médicale et biologique, eds Flammarion; Lazar and Schwartz, 1995, Elements de statistique médicale et biologique, eds Flammarion). The therapeutic efficacy of several agents may be evaluated in combination in the same assay.

15 Evaluation of the efficacy of a therapeutic agent using an animal model: there are injected into an animal fractions of purified urine and/or at least one polypeptide of the invention and/or at least one
 20 protein obtained by genetic recombination which corresponds to at least one polypeptide of the invention and/or at least one synthetic polypeptide whose amino acid sequence corresponds to the sequence of at least one polypeptide of the invention. The
 25 injections are carried out, at various established concentrations, into mammalian animals such as mice or rats, preferably a Lewis rat according to the protocol described in patent application W097/33466 cited above. Various concentrations of a fraction of crude or
 30 purified urine or of at least one polypeptide and/or one protein, as defined above, are injected into a series of animals by the intradermal, intravenous, intrathecal, intracerebral or intramuscular route, and the like. A negative control is carried out in
 35 parallel. The prophylactic and/or therapeutic agent to be evaluated and then injected at various concentrations and by various routes of administration to a mammalian animal, preferably to a mouse or to a rat. The injections are carried out as a single dose or

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as repeated doses, with various time intervals between each administration. A few hours to a few weeks after the administration, biological samples, preferably of blood, serum, cerebrospinal fluid, or urine, are collected. These samples are subjected to:

5 (i) a measurement of the gliotoxic activity by the bioassay, and/or

(ii) a measurement of activity of the polypeptides and/or proteins of interest of the invention, alone or

10 in combination, as described at least in: Li et al., 1983, Am J Hum Genet 35:629-634; Li et al., 1988 J Biol Chem 263:6588-6591; Li et al., 1981 J Biol Chem 256:6234-6240; Li et al., 1976 J Biol Chem 251:1159; Kase et al., 1996, FebsLetters 393: 74-76; Kishimoto et al.,

15 1992, J Lipid Res 33: 1255-1267; O'Brien et al., 1991 Faseb J 5: 301-308; Murthy et al., 1993 J Immunol 151: 6291-6301; Murao et al., 1990 Cell growth Differ 1: 447-454, and/or

(iii) an assay of the polypeptides and/or proteins of

20 interest, alone or in combination, by ELISA (Enzyme Linked-Immunsorbant Assay) and/or Western blotting, using antibodies or antibody fragments capable of binding to at least one of the polypeptides and/or proteins of the invention, or their fragment, and/or

25 (iv) an assay of antibodies specific for the polypeptides and/or proteins of interest or their fragments, alone or in combination or the assay of at least one ligand capable of binding to the polypeptides and/or proteins of interest or their fragments, and/or

30 (v) an assay of the "helper" and/or cytotoxic cellular immune response induced against the polypeptides and proteins of interest or their fragments and any immunogenic peptide derived from these polypeptides, proteins and fragments, by carrying out, for example, a

35 test of activation *in vitro* of "helper" T lymphocyte cells specific for the antigen administered; by quantifying the cytotoxic T lymphocytes according to the so-called ELISPOT technique described by Scheibenbogen et al., 1997 Clinical Cancer Research 3:

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221-226. Such a determination is particularly advantageous when it is desired to evaluate the efficacy of a vaccine approach for use in a given patient or for diagnosing and/or prognosticating a potential pathological condition by seeking to demonstrate an immune response naturally developed by the patient against the antigen, the polypeptides, the proteins of interest or the immunogenic fragments derived from these proteins.

10

The expression "ligand capable of binding to a protein" is understood to mean any molecule capable of recognizing the protein or a portion of the protein. This may be verified for example *in vitro* by Elisa and/or Western blot tests.

15

The expression "polypeptides and/or proteins of interest of the invention" designates the C-terminal fragment of Perlecan (SEQ ID No. 2), the precursor of the retinol-binding plasma protein (SEQ ID No. 4), the GM2 activator protein (SEQ ID No. 8), the mutated protein of the GM2 activator (SEQ ID No. 9), calgranulin B (SEQ ID No. 17), saposin B (SEQ ID No. 24), the proteins or fragments belonging to the family of the precursor of the retinol-binding plasma protein (for example SEQ ID No. 5 to 7), the proteins or fragments belonging to the family of the GM2 activator protein (for example SEQ ID No. 10 to 16), the proteins or fragments belonging to the family of calgranulin B protein (for example SEQ ID No. 18 to 23), the proteins or fragments belonging to the family of the saposin B protein (for example SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29.

35

The animal is then sacrificed and histological sections of various tissues are prepared, preferably brain

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sections. Various studies and observations are carried out in order to detect and/or quantify the characteristic effects of the polypeptides and/or active proteins associated with the gliotoxic fraction, that is to say an apoptosis of the glial cells, and/or the opening of the blood-brain barrier and/or a demyelination. The presence or the expression of the polypeptides and/or proteins of interest identified is also observed and/or quantified in these tissues:

10 (i) by conventional immunohistological analyses using ligands for the polypeptides and/or proteins of interest and/or their fragments and/or monoclonal or polyclonal antibodies or fragments of said which bind to the polypeptides and/or proteins of interest, or to

15 their fragments, and/or

(ii) by conventional *in situ* hybridization techniques using nucleic acid fragments or oligonucleotides defined from polypeptide and/or protein sequences of interest; and/or

20 (iii) by PCR and/or RT-PCR amplification techniques *in situ* using nucleic acid fragments or primers defined from polypeptide and/or protein sequences of interest.

The expression antibodies capable of binding to a polypeptide, to a protein or to their fragments is understood to mean any monoclonal or polyclonal antibody and any fragment of said antibodies capable of recognizing the polypeptide, the protein or their fragments. The capacity of the antibodies to recognize said polypeptides, proteins or their fragments is verified *in vitro*, for example by ELISA and/or Western blotting. An antibody capable of binding to the saposin B protein (SEQ ID No. 24) or to any fragment of this protein is described by Misasi et al. 1998, J. NeuroChem. 71:2313 and Klein et al. 1994, BBRC 200: 1440-1448 or may be produced using conventional methods, for example those designated by references above for the production of monoclonal and polyclonal antibodies, by immunization starting with a natural

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protein, a recombinant protein, a synthetic polypeptide or their fragments. The immunogenic peptides for the production of anti-saposin B monoclonal antibodies are the peptides corresponding to the sequences SEQ ID No. 5 61 and SEQ ID No. 62.

For example, an antibody capable of binding to the GM2 activator protein (SEQ ID No. 8) or to any fragment of this protein is illustrated by Yuziuk et al., 1998 J Biol Chem 273: 66-72 or may be produced using conventional methods known to persons skilled in the art. This antibody may for example be produced after injecting into mice or rabbits the natural protein or any fragment, and/or the recombinant protein or any fragment, and/or peptides defined and synthesized from the protein sequence of the protein. The immunogenic peptides used for the production of anti-GM2 monoclonal antibodies are the reference peptides SEQ ID No. 58, SEQ ID No. 59 and SEQ ID No. 60. An antibody capable of binding to the galgranulin B protein (SEQ ID No. 17) or to any fragment of this protein is described by Saintigny et al., 1992 J Invest Dermatol 99: 639-644 and Goebeler et al. 1994 J Leukoc Biol 55: 259-261, or may be produced using conventional methods. The immunogenic peptides for the production of anti-calgranulin B monoclonal antibodies are the peptides corresponding to the sequences SEQ ID No. 63, SEQ ID No. 64 and SEQ ID No. 65. An antibody capable of binding to the mutated GM2 activator protein (SEQ ID No. 9) or to any fragment of this protein may be produced using the conventional methods defined above.

The expression natural protein and fragment is understood to mean any isolated, completely or partially purified protein obtained from a human or animal sample and any fragment obtained from this protein. For example, the natural protein corresponding to saposin B (SEQ ID No. 24) is obtained according to the technique described by Waring et al. 1998 Mol Genet

Metab 63: 14-25; the natural protein corresponding to the GM2 activator protein (SEQ ID No. 8) according to the technique described by DeGasperi et al., 1989 Biochem J 260: 777-783, Vogel et al., 1987 Arch Biochem Biophys 259: 627-638, Mitsuyama, 1983 Hokkaido Igaku Zasshi 58: 502-512; Hirabayashi et al 1983 J Neurochem 40: 168-175, Conzelmann et al., 1979 Hoppe Seylers Z Physiol Chem 360: 1837-1849, Li et al., 1976 J Biol Chem 251: 1159-1163. The natural protein corresponding to calgranulin B (SEQ ID No. 17) is obtained according to the technique described by Hitomi et al., 1996 J Cell Sci 109: 805-815, Van den Bos et al. 1998 Protein Expr Purif 13: 313-318 and Raftery et al. 1996 Biochem J 316: 285-293.

15 The expression recombinant protein or fragment of a recombinant protein refers to any protein or protein fragment produced in a prokaryotic or eukaryotic cell from a nucleotide sequence encoding the protein or its fragment and transfected into the cell, this protein or its fragment then being purified. In general, any cell derived from a prokaryotic or eukaryotic organism may be used in the context of the present invention, but the cells derived from eukaryotic organisms are preferred. There may be mentioned, by way of example, CHO cells, COS cells, and Semliki cells. For the purposes of the present invention, said cell may be wild type or mutant. For example, the recombinant protein corresponding to saposin B (SEQ ID No. 24) may be obtained according to the techniques described by Zaltash et al. 1998 Bebb's letter 423: 1-4 and Qi et al. 1994 J Biol Chem 269: 16746-16753. Such a recombinant protein is at least available from Kase et al. 1996 Febs Lett 393: 74-76. The recombinant protein corresponding to the GM2 activator protein (SEQ ID No. 8) may be produced by the techniques described by Yuziuk et al. 1998 J Biol Chem 273: 66-72 and Bierfreund et al., 1999 Neurochem Res 24: 295-300. The recombinant protein corresponding to calgranulin B (SEQ

ID No. 17) may be obtained according to the protocol by Longbottom et al. 1992 Biochim Biophys Acta 1120:215-222, Raftery et al. 1999 Protein Expr Purif 15:228-235. Such a recombinant protein is available at least from
5 Klempt et al. 1997 Febs Letter 408:81-84.

The expression DNA nucleotide sequence or DNA nucleotide fragment encoding all or part of the saposin B protein (SEQ ID No. 24) is understood to mean the
10 nucleic acid sequence SEQ ID No. 53 or a fragment of this sequence. The expression RNA nucleotide sequence or fragment encoding all or part of the saposin B protein (SEQ ID No. 24) is understood to mean any sequence deduced from the DNA sequence SEQ ID No. 53,
15 taking into account the genetic code and the splicing phenomena.

The expression DNA nucleotide sequence or DNA nucleotide fragment encoding all or part of the GM2
20 activator protein (SEQ ID No. 8) is understood to mean the nucleic acid sequence SEQ ID No. 31 or a fragment of this sequence. The expression RNA nucleotide sequence or fragment encoding all or part of the GM2 activator protein (SEQ ID No. 8) is understood to mean
25 any sequence deduced from the DNA sequence SEQ ID No. 31, taking into account the genetic code and the splicing phenomena.

The expression DNA nucleotide sequence or DNA
30 nucleotide fragment encoding all or part of the calgranulin B protein (SEQ ID No. 17) is understood to mean the nucleic acid sequence SEQ ID No. 42 or a fragment of this sequence. The expression RNA nucleotide sequence or fragment encoding all or part of
35 the calgranulin B protein (SEQ ID No. 17) is understood to mean any sequence deduced from the DNA sequence SEQ ID No. 42, taking into account the genetic code and the splicing phenomena.

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The expression nucleotide sequence or fragment encoding all or part of the mutated protein (SEQ ID No. 9) is understood to mean the nucleic acid sequence deduced from the sequence SEQ ID No. 9, taking into account the genetic code. The expression RNA nucleotide sequence or fragment encoding all or part of this mutated B protein (SEQ ID No. 9) is understood to mean any sequence deduced from the DNA sequence, taking into account the genetic code and the splicing phenomena.

10

The expression protein activity is understood to mean a characteristic biological function of the protein. The protein activity may be demonstrated by techniques known to persons skilled in the art. For example, the activity of saposin B (SEQ ID No. 24) and of the proteins of the saposin B family (for example SEQ ID No. 25 to 29) may be detected using the protocols described by Li et al., 1983, Am J Hum Genet 35:629-634; Li et al., 1988 J Biol Chem 263: 6588-6591, Li et al., 1981 J Biol Chem 256: 6234-6240 and Li et al., 1976 J Biol Chem 251:1159. The expression activity of the GM2 activator protein (SEQ ID No. 8) and of the proteins of the same family (for example SEQ ID No. 10 to 16) is understood to mean at least the activity detected using the protocols described, for example, by Kase et al., 1996, Febs Letters 393: 74-76, Kishimoto et al., 1992, J Lipid Res 33:1255-1267 and O'Brien et al., 1991 Faseb J 5: 301-308. The expression activity of calgranulin B (SEQ ID No. 17) and the proteins of the same calgranulin B family (for example SEQ ID No. 18 to 23) and any is understood to mean at least the activity detected using the protocols described for example by Murthy et al., 1993 J Immunol 151: 6291-6301 and Murao et al., 1990 Cell growth Differ 1: 447-454.

35

Production of a transgenic animal, preferably murine, model for a human pathology can be technically achieved. Briefly, the transgenic animal is produced using the conventional techniques described and

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possesses, integrated into the genome, the nucleic acids encoding the proteins or their fragments.

Evaluation of the efficacy of a therapeutic agent and
5 therapeutic monitoring *ex vivo*, in humans:

the therapeutic agents to be tested for a therapeutic activity and/or for therapeutic monitoring are administered by various routes to humans, such as the
10 intradermal, intravenous, intramuscular, intracerebral or oral routes, and the like. Various doses are administered to human beings. The patient's clinical file at the time of the first administration is perfectly known. One or more administrations may be
15 carried out with various time intervals between each administration which may range from a few days to a few years. Biological samples are collected at defined time intervals after administration of the therapeutic agent, preferably blood, serum, cerebrospinal fluid and
20 urine. Various analyses are carried out using these samples. Immediately before the first administration of the therapeutic agent, these sample collections and these same analyses are again performed. A conventional clinical and biological examination (MRI, oligoclonal
25 bands in cerebrospinal fluid, evoked potentials) is also carried out in 'parallel with the additional analyses which are described below, at various analytical times. The analyses carried out are:

- 30 (i) a measurement of the gliotoxic activity by bioassay starting with samples of serum, CSF and urine, and/or
- (ii) a measurement of the activity of proteins of interest identified in the present invention alone or in combination, as described for example by: Li et al.,
35 1983, Am J Hum Genet 35:629-634; Li et al., 1988 J Biol Chem 263: 6588-6591; Li et al., 1981 J Biol Chem 256: 6234-6240; Li et al., 1976 J Biol Chem 251:1159; Kase et al., 1996, FebsLetters 393:74-76; Kishimoto et al., 1992, J Lipid Res 33: 1255-1267; O'Brien et al., 1991

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Faseb J 5: 301-308; Murthy et al., 1993 J Immunol 151: 6291-6301; Murao et al., 1990 Cell growth Differ 1: 447-454; and/or

- (iii) an assay of the proteins of interest or of their
5 fragments, alone or in combination, in the blood/
serum, CSF or urine samples by ELISA and/or Western
blotting, using antibodies or antibody fragments
capable of binding to at least one of the proteins or
to one of their fragments, and/or
10 (iv) an assay of antibodies specific for the proteins
of interest or of their fragments in blood/serum, CSF
or urine samples, by ELISA and/or Western blotting
using a natural protein or a fragment of the natural
protein and/or a recombinant protein or a fragment of
15 this recombinant protein, alone or in combination.
Likewise, an assay of ligands capable of binding to the
proteins of interest identified, alone or in
combination, may be carried out, and/or
(v) an assay of "helper" and/or cytotoxic cellular
20 immune response induced against the proteins of
interest and any immunogenic peptide derived from these
proteins, for example by carrying out a test of
activation *in vitro* of T lymphocyte cells specific for
the antigen administered (example). For example, using
25 a test of activation *in vitro* of helper T lymphocyte
cells specific for the antigen administered (example);
For example by quantifying the cytotoxic T lymphocytes
according to the so-called ELISPOT technique described
by Scheibenbogen et al., 1997 Clinical Cancer Research
30 3: 221-226. Such a determination is particularly
advantageous when it is desired to evaluate the
efficacy of a vaccine approach used in a given patient
or to diagnose a potential pathological condition in a
patient, seeking to demonstrate an immune response
35 naturally developed by said patient against the
antigen, the proteins of interest or any immunogenic
fragment derived from these proteins, alone or in
combination, and/or

- (vi) a detection of DNA and/or RNA fragments encoding the proteins or a fragment of proteins of interest by nucleotide hybridization according to techniques well known to persons skilled in the art (Southern blotting, Northern blotting, ELOSA "Enzyme-linked Oligosorbent Assay" (Katz JB et al., Am. J. Vet. Res., 1993 Dec; 54 (12):2021-6 and Francois Mallet et al., Journal of Clinical Microbiology, June 1993, p1444-1449)) and/or by the DNA and/or RNA amplification method, for example by PCR, RT-PCR, using nucleic acid fragments encoding the sequence of the proteins of interest, and/or
- (vii) by tissue, preferably brain, biopsy and observation of the characteristic effects of the active proteins associated with the gliotoxic fraction, that is to say an apoptosis of the glial cells and/or the opening of the blood-brain barrier and/or the observation of demyelination phenomena, and/or
- (viii) by tissue biopsy or on circulating cells (blood, CSF), observation of the presence of proteins of interest and estimation of their expression by immunohistological observation on histological sections prepared from tissues, using ligands and/or antibodies or their fragments capable of binding to the proteins of interest, and/or
- (ix) by tissue biopsy or on circulating cells (blood, CSF), observation of the expression of the proteins of interest by in situ hybridization of the RNA molecules encoding the proteins of interest using nucleic acids defined using the sequences of the proteins of interest, and/or
- (x) by tissue biopsy or on circulating cells (blood, CSF), determination of the expression of the proteins of interest by amplification of these RNAs by conventional techniques such as, for example, RT-PCR, using nucleic acids defined using the sequences of the proteins of interest.

The expression "polypeptides and/or proteins of interest of the invention" designates the C-terminal

fragment of Perlecan (SEQ ID No. 2), the precursor of the retinol-binding plasma protein (SEQ ID No. 4), the GM2 activator protein (SEQ ID No. 8), the mutated GM2 activator protein (SEQ ID No. 9), calgranulin B (SEQ ID No. 17), saposin B (SEQ ID No. 24), the proteins or fragments belonging to the family of the precursor of the retinol-binding plasma protein (for example SEQ ID No. 5 to 7), the proteins or fragments belonging to the family of the GM2 activator protein (for example SEQ ID No. 10 to 16), the proteins or fragments belonging to the calgranulin B protein family (for example SEQ ID No. 18 to 23), the proteins or fragments belonging to the saposin B protein family (for example SEQ ID No. 25 to 29), and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29.

The expression DNA nucleic acid sequence or fragments encoding the "polypeptides and/or proteins of interest of the invention" designates the nucleic acid sequence encoding the C-terminal fragment of Perlecan (SEQ ID No. 2), the nucleic acid sequence encoding the precursor of the retinol-binding plasma protein (SEQ ID No. 4), the nucleic acid sequence (SEQ ID No. 31) encoding the GM2 activator protein (SEQ ID No. 8), the nucleic acid sequence encoding the mutated GM2 activator protein (SEQ ID No. 9), the nucleic acid sequence (SEQ ID No. 42) encoding calgranulin B (SEQ ID No. 17), the nucleic acid sequence (SEQ ID No. 53) encoding saposin B (SEQ ID No. 24), the DNA and RNA nucleic acid sequences (SEQ ID No. 30 to 57) encoding the proteins or fragments belonging to the family of the precursor of the retinol-binding plasma protein (for example SEQ ID No. 5 to 7), the proteins or fragments belonging to the family of the GM2 activator protein (for example SEQ ID No. 10 to 16), the proteins or fragments belonging to the calgranulin B protein family (for example SEQ ID No. 18 to 23), the proteins

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or fragments belonging to the saposin B protein family (for example SEQ ID No. 25 to 29).

A protein or a variant of a protein chosen more particularly from the sequences defined in the identifiers SEQ ID Nos. 2, 4, 8, 9, 17 and 24 or their fragments, or from the sequences corresponding to the proteins of the families of said sequences (SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 24, SEQ ID No. 25 to 29), and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29, independently or in combination, exhibits a toxic effect directly or indirectly on cells, in particular on glial cells, which is demonstrated by the abovementioned bioassay. The autoantibodies produced in response to the presence of this protein or of these proteins are associated with the autoimmune process. Thus, the target of the therapeutic agent(s) is for example (i) the natural protein or the natural proteins or their variants with the aim of regulating their expression and/or their intracellular concentration and/or their concentration in the bloodstream, (ii) an antibody specific for at least such a protein. The therapeutic agent or the therapeutic agents defined eliminate the target directly, by inducing a specific immune response, and/or neutralize it.

The present invention therefore relates to a biological material for the preparation of a pharmaceutical composition for treating mammals suffering from degenerative and/or autoimmune and/or neurological pathological conditions, preferably multiple sclerosis, said composition comprising:

(i) either at least one natural protein and/or one recombinant protein or their fragments whose sequence corresponds to all or part of the sequences designated

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by the references SEQ ID No. 2, 4, 8, 9, 17 and 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29), and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29, independently or in combination,

(ii) or at least one ligand specific for at least one of said proteins or their fragments whose sequence corresponds to all or part of the sequences designated by the references SEQ ID No. 2, 4, 8, 9, 17 and 24, and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29), and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29, independently or in combination,

(iii) or at least one polyclonal or monoclonal antibody specific for at least one of said proteins or their fragments whose sequence corresponds to all or part of the sequences designated by the references SEQ ID No. 2, 4, 8, 9, 17 and 24, and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the

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ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29), and the peptide sequences which exhibit
5 at least 70% identity, preferably at least 80% identity and advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29, independently or in combination,

10 (iv) or at least one nucleic acid sequence comprising at least one gene of therapeutic interest whose nucleic sequence is deduced from the DNA and RNA sequences encoding all or part of the proteins whose sequences are designated by the references SEQ ID No. 2, 4, 8, 9,
15 17 and 24, and the DNA and/or RNA sequences (for example SEQ ID No. 30 to 57) encoding all or part of the proteins belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the GM2 activator,
20 calgranulin B and saposin B, in association with elements ensuring the expression of said gene of therapeutic interest *in vivo* in target cells intended to be genetically modified by the nucleic sequence of the gene of therapeutic interest,

25 (v) or at least one mammalian cell not naturally producing the protein of interest or the proteins of interest or any fragment of this or these protein(s) or of the antibodies specific for at least one of said
30 proteins or of its fragments, said mammalian cell being genetically modified *in vitro* by at least one nucleic acid sequence or a fragment of a nucleic acid sequence or a combination of nucleic acid sequences corresponding to nucleic acid fragments derived from
35 the same gene or from different genes, said nucleic sequence(s) being deduced from the DNA and RNA sequences encoding the proteins designated by the references SEQ ID No. 2, 4, 8, 9, 17 and 24, and the DNA and/or RNA sequences (for example SEQ ID No. 30 to

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57) encoding all or part of the proteins belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the GM2 activator, calgranulin B and saposin B, said gene of therapeutic interest encoding all or part of the protein of interest, of a fragment of the protein of interest or of an antibody specific for the protein of interest which will be expressed at the surface of said mammalian cell (Toes et al., 1997, PNAS 94: 14660-14665). The pharmaceutical composition may contain a therapeutic agent alone directed against a target alone or agents taken in combination directed against several targets.

15 The expression "polypeptides and/or proteins of interest of the invention" designates the C-terminal fragment of Perlecan (SEQ ID No. 2), the precursor of the retinol-binding plasma protein (SEQ ID No. 4), the GM2 activator protein (SEQ ID No. 8), the mutated GM2 activator protein (SEQ ID No. 9), calgranulin B (SEQ ID No. 17), saposin B (SEQ ID No. 24), the proteins or fragments belonging to the family of the precursor of the retinol-binding plasma protein (for example SEQ ID No. 5 to 7), the proteins or fragments belonging to the family of the GM2 activator protein (for example SEQ ID No. 10 to 16), the proteins or fragments belonging to the calgranulin B protein family (for example SEQ ID No. 18 to 23), the proteins or fragments belonging to the saposin B protein family (for example SEQ ID No. 25 to 29 and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29.

35 From the knowledge of the amino acid sequences of the proteins of interest identified in the present invention, it is within the capability of persons skilled in the art to define and use the molecules described above and/or any molecule capable of binding

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to said molecules, and/or any molecule capable of inhibiting said molecules. Thus, the present invention relates to the use of natural and/or recombinant proteins and/or of synthetic polypeptides and their
5 fragments, of ligands capable of binding to said proteins or to their fragment(s), for example antibodies; proteins inhibiting the function and/or expression and/or binding of said proteins.

10 Use of natural protein(s) and/or peptide(s) and/or recombinant protein(s) and/or synthetic polypeptide(s) corresponding to the proteins of interest identified in the present invention.

15 The present invention relates to a biological material for the preparation of pharmaceutical compositions for treating mammals suffering from an autoimmune disease, preferably multiple sclerosis, comprising:

20 (i) either at least one natural protein and/or one recombinant protein and/or one synthetic polypeptide chosen from the proteins whose amino acid sequences are designated by the references SEQ ID No. 2, 4, 8, 9, 17 and 24, and the peptide sequences or the fragments of
25 said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID
30 No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29), and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29, alone or in
35 combination,

(ii) or at least one natural and/or synthetic fragment of these proteins of interest, for example an

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immunogenic fragment capable of inducing an immune response against a target polypeptide,

(iii) or at least one mimotope peptide defined from the reference sequences SEQ ID No. 2, 4, 8, 9, 17 and 24, and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29), and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29, or a combination of mimotopes, capable of inducing an immune response against the target polypeptide,

(iv) or at least any protein or peptide capable of regulating *in vivo* the transcription and/or the translation of the proteins of interest (SEQ ID No. 2, 4, 8, 9, 17 and 24) and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29. The administration of these proteins and/or peptides alone or in combination can reestablish the concentration of a protein of interest in the body.

The immune response directed against a specific antigen may be divided into two distinct categories, one

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involving the antibodies (humoral type immune response), the other the cytotoxic effector cells such as for example the macrophages, the cytotoxic lymphocytes (CTL) or the killer (NK) cells as well as the "helper" T lymphocytes, in particular the CD4+ T lymphocytes (cellular type immune response). More particularly, the two types of response are distinguishable in that the antibodies recognize the antigens under their three-dimensional form whereas the T lymphocytes, for example, recognize peptide portions of said antigens, associated with glycoproteins encoded by the genes of the major histocompatibility complex (MHC), in particular the genes of the type I major histocompatibility complex which are ubiquitously expressed at the surface of the cells or the genes of the type II major histocompatibility complex which are specifically expressed at the surface of the cells involved in the presentation of antigens (APC).

1) According to a first aspect, the cellular type immune response is characterized in that the CD4+ type T cells (helper T cells), following a well-known activation phenomenon (for a review see Alberola 1997, Annu Rev Immunol 15, 125-154), produce cytokines which in turn induce the proliferation of APC cells capable of producing said cytokines, the cellular differentiation of the B lymphocytes capable of producing antibodies specific for the antigen, and the stimulation of the cytotoxic T lymphocytes (CTL).

2) According to a second aspect of the cellular immune response, the cytotoxic effector cells such as for example the CD8+ type lymphocytes (CTL) are activated a) after interaction with antigenic peptides bound to and presented by the glycoproteins carried by the ubiquitous cells and encoded by the genes belonging to the MHCI system, and b) optionally by the cytokines produced by the CD4+ cells.

The present invention relates to the administration of a protein or of a peptide derived from the proteins of

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interest (SEQ ID No. 2, 4, 8, 9, 17 and 24) or of their fragment(s), and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29), and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, alone or in combination, for the prophylaxy and/or the therapy of an autoimmune disease, such as multiple sclerosis. These administered proteins and peptides are characterized in that they must have lost their toxic activity, for example their gliotoxic activity, or must have lost their capacity to bind to a ligand, and may significantly induce an immune response mediated by the T lymphocytes and/or the antibodies directed against this protein are used. Such proteins are said to be "modified"; nevertheless, their immunogenicity is preserved. Such modified immunogenic molecules are obtained by a number of conventional treatments, for example chemical or heat denaturation, truncation or mutation with deletion, insertion or location of amino acids. An example of truncation consists in the truncation of amino acids at the carboxy-terminal end which may be up to 5-30 amino acids. The modified molecules may be obtained by synthetic and/or recombinant techniques or by chemical or physical treatments of the natural molecules.

The natural and/or recombinant proteins of interest identified in the present invention (SEQ ID No. 2, 4, 8, 9, 17 and 25), and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the

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ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29), and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98 identity with any one of the peptide sequences SEQ ID No. 1 to 29, or their fragment(s), are used in prophylactic and therapeutic vaccination against autoimmune diseases, preferably MS.

10 A vaccine comprises an immunogenically effective quantity of the immunogenic protein in association with a pharmaceutically acceptable vehicle and optionally an adjuvant and/or a diluent. The pharmaceutically acceptable vehicles, adjuvants and diluents are well known to persons skilled in the art. There may be mentioned, by way of references, Remington's Pharmaceutical Sciences. The use of vaccine compositions is particularly advantageous in association with an early diagnosis of the disease. The immunogenic protein is used in the preparation of a medicament for prophylactic or therapeutic vaccination. The proteins of interest may be eliminated from the body without inducing undesirable side effects. The identification of such vaccine proteins or peptides is carried out as follows: the candidate molecules modified as described above (proteins which are natural or recombinant, peptides) are analyzed in a functional test to verify that they have lost their toxicity, for example their gliotoxic activity, using the test known as bioassay, and to verify their immunogenicity (i) by carrying out an *in vitro* test of proliferation of CD4+ T lymphocytes specific for the antigen administered (T cell assay) or an *in vitro* test of cytotoxicity of the CD8+ lymphocytes specific for the antigen administered and (ii) by measuring, inter alia, the amount of circulating antibodies directed against the natural protein. These modified forms are used to immunize humans by standard procedures with appropriate adjuvants.

The prepared vaccines are injectable, that is to say in liquid solution or in suspension. Optionally, the preparation may also be emulsified. The antigenic molecule may be mixed with excipients which are pharmaceutically acceptable and compatible with the active ingredient. Examples of favorable excipients are water, saline solution, dextrose, glycerol, ethanol or equivalents and their combinations. If desired, the vaccine may contain minor quantities of auxiliary substances such as "wetting" or emulsifying agents, pH buffering agents or adjuvants such as aluminum hydroxide, muramyl dipeptide or variations thereof. In the case of peptides, their coupling to a larger molecule (KLH, tetanus toxin) sometimes increases the immunogenicity. The vaccines are conventionally administered by injection, for example by subcutaneous or intramuscular injection. Additional formulations favorable with other modes of administration include suppositories and sometimes oral formulations.

In general, the concentration of the polynucleotide in the composition used for administration *in vivo* is from 0.1 µg/ml up to 20 mg/ml. The polynucleotide may be homologous or heterologous for the target cell into which it will be introduced.

The present invention also relates to the use of vaccines including molecules of nucleic acids which encode the proteins of interest or immunogenic peptides or their fragment(s), which are non-active, corresponding to the proteins of interest (SEQ ID No. 2, 4, 8, 9, 17 and 24) and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID

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No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29. The
5 nucleic acid vaccines, in particular the DNA vaccines, are generally administered in association with a pharmaceutically acceptable vehicle by intramuscular injection.

10 From the amino acid sequence of the proteins of interest described (SEQ ID No. 2, 4, 8, 9, 17 and 24) and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-
15 binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70%
20 identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, peptides or fragments corresponding to all or part of the primary sequence of these proteins may be synthesized by
25 conventional methods of peptide synthesis or obtained by genetic recombination.

Recombinant proteins corresponding to the proteins of interest, produced in a prokaryotic or eukaryotic
30 cellular system, are available from various teams and are described in the literature. They may also be produced by persons skilled in the art from the knowledge of the sequences of the corresponding genes described in the literature and taking into account the
35 degeneracy of the genetic code. All the protein sequences identified in the present invention are thus capable of being obtained by genetic recombination. The genes are cloned into suitable vectors. Different vectors are used to transform prokaryotic cells (for

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example *E. coli*) and eukaryotic cells (for example COS cells, CHO cells and Simliki cells). The recombinant proteins corresponding to the proteins of interest or to fragments of the proteins of interest may thus be
5 produced in prokaryotic and/or eukaryotic cellular systems. In *E. coli* cells, the recombinant proteins are produced with a polyhistidine tail. The insoluble protein fraction is solubilized in 8M urea. Enrichment of the product was carried out on nickel-chelated resin
10 (Qiagen). The column was washed with decreasing concentrations of urea. The elution was carried out with imidazole in the absence of urea. The complete sequence of the proteins of interest may also be cloned into a suitable plasmid and then transferred into the
15 vaccinia virus in order to obtain a recombinant virus.

Use of ligands capable of binding to the proteins of interest identified in the present invention.

20 The present invention relates to a biological material for the preparation of pharmaceutical compositions for treating mammals suffering from an autoimmune disease, preferably multiple sclerosis, comprising:

25 (i) either at least one ligand capable of binding to the proteins and/or fragments of the proteins chosen from the target proteins SEQ ID No. 2, 4, 8, 9, 14 and 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins
30 chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29)
35 and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, the ligand

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being capable or not of inhibiting the protein activity,

(ii) or at least one polyclonal or monoclonal antibody
5 capable of binding to at least one protein or one of
its fragments chosen from the target proteins SEQ ID
No. 2, 4, 8, 9, 14 and 24 and the peptide sequences or
the fragments of said sequences belonging to the same
family of proteins chosen from Perlecan, the precursor
10 of the retinol-binding plasma protein, precursor of the
ganglioside GM2 activator, calgranulin B and saposin B
(for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5
to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID
No. 25 to 29) and the peptide sequences which exhibit
15 at least 70% identity, preferably at least 80% identity
and advantageously at least 98% identity with any one
of the peptide sequences SEQ ID No. 1 to 29. This
antibody may be neutralizing or not, that is to say
capable or not of inhibiting the activity of the
20 protein of interest. The ligand may be chosen from any
molecule or molecule fragment capable of binding to the
target proteins, for example the receptor for this
proteins, the cofactors for these proteins, the
polyclonal or monoclonal antibodies capable of binding
25 to the proteins or any fragment of these proteins.

These antibodies are very useful in particular for
allowing the use of therapeutic compositions because
they lead, for example, to immune reactions directed
30 specifically against immunodominant epitopes or against
antigens exhibiting high variability. There are
administered to the patient either neutralizing soluble
antibodies in order to inhibit their function, or
specific soluble antibodies in order to eliminate the
35 peptide by formation of immune complexes. The invention
describes the use of antibodies capable of specifically
recognizing at least one protein described in the
present invention for the treatment and/or for the
therapeutic monitoring of a degenerative and/or

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neurological and/or autoimmune disease, preferably multiple sclerosis. These antibodies are polyclonal and preferably monoclonal. Preferably, these antibodies recognize the active site of the protein and, upon
5 binding, inhibits the function of the protein. The capacity of the antibody to specifically bind to the protein is analyzed by conventional techniques which have been described, such as for example by ELISA or Western blot tests using the natural or synthetic
10 immunogenic peptide or protein. The antibody titer is determined. The capacity of the antibody to neutralize the function of the protein may be analyzed by various means, for example by determining the reduction in the activity of the immunogenic peptide or protein in the
15 presence of antibodies, preferably by determining the reduction in the gliotoxic activity using the bioassay test *in vitro*.

For example, the monoclonal antibodies directed against
20 the target protein or a portion of this protein are produced by conventional techniques used to produce antibodies against surface antigens. Mice or rabbits are immunized (i) either with the natural or recombinant protein of interest, (ii) or with any
25 immunogenic peptide of this protein of interest, (iii) or with murine cells which express the protein or the peptide of interest and the MHCII molecules.

The Balb/c murine line is the most frequently used. The immunogen is also a peptide chosen from the peptides
30 defined from the primary sequences of the proteins of interest. For example, the following immunogen was prepared: the peptides SEQ ID Nos. 58, 59, 60 derived from the sequence of the precursor of the ganglioside GM2, the peptides SEQ ID Nos. 61, 62 derived from the
35 sequence of saposin B and the peptides SEQ ID Nos. 63, 64, 65 derived from calgranulin B were coupled to Keyhole Lymphet hemocyanin, abbreviated peptide-KLH, as support for its use in immunization, or coupled to human serum albumin, abbreviated peptide-HSA. The

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animals were subjected to an injection of peptide-KLH or of peptide-HSA using complete Freund's adjuvant (CFA). The sera and the hybridoma culture supernatants derived from animals immunized with each peptide were
5 analyzed for the presence of anti-protein antibodies by an ELISA test using the initial proteins. The spleen cells of these mice were consequently recovered and fused with myeloma cells. Polyethylene glycol (PEG) is the fusion agent most frequently used. The hybridomas
10 producing the most specific and the most sensitive antibodies are selected. The monoclonal antibodies may be produced *in vitro* by cell culture of the hybridomas produced or by recovering murine ascitic fluid after intraperitoneal injection of the hybridomas in mice.
15 Whatever the mode of production, in supernatant or in ascites, it is then important to purify the monoclonal antibody. The methods of purification used are essentially ion-exchange gel filtration or exclusion chromatography, or even immunoprecipitation. For each
20 antibody, the method which will make it possible to obtain the best yield should be chosen. A satisfactory number of anti-protein antibodies are targeted in functional tests in order to identify the most efficient antibodies for binding the protein of
25 interest and/or for blocking the activity of the protein of interest. The monoclonal antibodies selected are humanized by standard "CDR grafting" methods (protocol performed by many companies, as a service). These humanized antibodies may be clinically tested in
30 the patient. The efficiency of these antibodies may be monitored by clinical parameters.

The *in vitro* production of antibodies, of antibody fragments or of antibody derivatives, such as chimeric
35 antibodies, produced by genetic engineering, in eukaryotic cells has been described (EP 120 694 or EP 125 023) and is also applicable to the present invention.

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Use of molecules inhibiting the proteins of interest identified in the present invention.

The present invention relates to a biological material
5 for the preparation of pharmaceutical compositions for
treating mammals suffering from a degenerative and/or
neurological and/or autoimmune disease, preferably
multiple sclerosis, said composition comprising
10 (i) either at least one molecule inhibiting the
function of at least one protein chosen from the
proteins identified in the present invention (SEQ ID
No. 2, 4, 8, 9, 17, 24) and the peptide sequences or
the fragments of said sequences belonging to the same
family of proteins chosen from Perlecan, the precursor
15 of the retinol-binding plasma protein, precursor of the
ganglioside GM2 activator, calgranulin B and saposin B
(for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5
to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID
No. 25 to 29) and the peptide sequences which exhibit
20 at least 70% identity, preferably at least 80% identity
and advantageously at least 98% identity with any one
of the peptide sequences SEQ ID No. 1 to 29, for
example inhibiting the gliotoxic activity, (ii) or at
least one molecule regulating the expression of at
25 least one protein chosen from the proteins SEQ ID
No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the
fragments of said sequences belonging to the same
family of proteins chosen from Perlecan, the precursor
of the retinol-binding plasma protein, precursor of the
30 ganglioside GM2 activator, calgranulin B and saposin B
(for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5
to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID
No. 25 to 29) and the peptide sequences which exhibit
at least 70% identity, preferably at least 80% identity
35 and advantageously at least 98% identity with any one
of the peptide sequences SEQ ID No. 1 to 29, for
example to block transcription or translation, (iii) or
at least one molecule regulating the metabolism of at
least one protein chosen from the proteins SEQ ID

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No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, (iv) or at least one molecule regulating the expression and/or the metabolism of a ligand for at least one protein chosen from the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to SEQ ID No. 8 and SEQ ID No. 10 to 29 and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, for example a receptor or a cofactor. It is also possible to think that these proteins of the human body can be inhibited with no side effect.

Another important aspect of the invention relates to the identification and the evaluation of the therapeutic efficacy of natural and/or synthetic substances (i) capable of blocking and/or inhibiting the activity of the proteins of interest of the invention and/or of their fragment: SEQ ID No. 2, 4, 8,

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9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29 and/or (ii) capable of inhibiting their metabolism such as the inhibitors of the corresponding metabolism, the inhibitors of enzymes activated by the coenzymes, (iii) capable of regulating the expression of the proteins of interest (SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, (iv) capable of inhibiting the function and/or the expression of the ligands for the proteins of interest SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one

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of the peptide sequences SEQ ID No. 1 to 29, such as for example receptors. These substances may be used in prophylactic or therapeutic treatments of the disease. The invention also relates to methods for treating and preventing an autoimmune disease, for example MS, by administering effective quantities of these substances. The substances may be proteins, antibodies, small synthetic or natural molecules, derivatives of the proteins identified in this invention, lipids, glycolipids and the like. The small molecules may be screened and identified in a large quantity using chemical combinatorial libraries. The invention also relates to pharmaceutical compositions comprising these substances in association with acceptable physiological carriers, and methods for the preparation of medicaments to be used in the therapy or in the prevention of autoimmune diseases including MS using these substances.

To identify inhibitory molecules of low molecular weight such as candidate drugs for degenerative and/or neurological and/or autoimmune diseases, such as multiple sclerosis, there are used the tests and protocols described in above and in the patent applications incorporated by way of reference, using samples collected from untreated or treated patients, untreated or treated animal models, or tissues of untreated or treated animal models. This aspect of the invention also includes a method for identifying substances capable of blocking or inhibiting the activity of the proteins of interest, comprising the introduction of these substances into a test *in vitro* or into an animal model *in vivo*. The molecules selected are tested at different concentrations. These inhibitors are also tested in toxicity and pharmacokinetic assays to know if they can represent valid candidate drugs. The substances tested for the inhibition or the blocking of the protein activities or for the expression of the proteins, in these screening

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procedures, may be proteins, antibodies, antibody fragments, small synthetic or natural molecules, derivatives of the proteins of interest and the like. The small molecules may be screened and identified in a
5 large quantity using chemical combinatorial libraries.

By way of example, there may be mentioned as inhibitory substances:

10 The inhibitors of the proteins identified in the present invention (SEQ ID No. 2, 4, 8, 9, 17, 24), the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma
15 protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity,
20 preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, and the inhibitors of the fragments of said proteins. These inhibitors may be included in a prophylactic and therapeutic composition,
25 in particular for the treatment of multiple sclerosis. For example, lycorine, an alkaloid extracted from Amaryllidaceae (e.g.: *Crinum asiaticum*) is used *in vitro* at a concentration of between 0.1 and 0.5 µg/ml and *in vivo* at a concentration of between 0.1
30 and 1 mg/kg/day. For example, Rolipram (trade name) and Ibudilast (trade name), which are two molecules of the same family of inhibitors of 4(PDE4) phosphodiesterases, are used *in vitro* at concentrations of between 1 and 10 µM/l and *in vivo* at concentrations
35 of between 10 mg/kg/day.

From the amino acid sequences of the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same

chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, or their fragment(s), (ii) or at least one nucleic acid sequence comprising at least one gene of therapeutic interest encoding the proteins or a fragment of proteins (SEQ ID No. 2, 4, 8, 9, 17, 24), the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, and elements ensuring the expression of said gene *in vivo* in target cells intended to be genetically modified by said nucleic sequence.

The expression nucleic acid sequence is understood to mean a DNA and/or RNA fragment which is double-stranded or single-stranded, linear or circular, natural and isolated or synthetic, designating a precise succession of nucleotides, modified or otherwise, which makes it possible to define a fragment or a region of a nucleic acid chosen from the group consisting of a cDNA; a genomic DNA; a plasmid DNA; a messenger RNA. These nucleic acid sequences are deduced from the amino acid sequence of the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins

chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, using the genetic code. Because of the degeneracy of the genetic code, the invention also encompasses equivalent or homologous sequences. These defined sequences allow persons skilled in the art themselves to define the appropriate nucleic acids.

Accordingly, the present invention relates to a biological material for the preparation of pharmaceutical compositions comprising at least one nucleic acid sequence capable of hybridizing with a nucleic acid sequence encoding the proteins of interest or their fragment(s) (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29.

The invention consists in defining and using nucleic acid molecules complementary to the DNA and/or RNA sequences encoding the proteins of interest or their fragment(s). These fragments correspond to ribozyme or antisense molecules and may be synthesized using automated synthesizers, such as those marketed by the

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company Applied Biosystem. The invention describes the use of these nucleic acids capable of hybridizing under stringent conditions with the DNA and/or RNA encoding the proteins of the invention or their fragment(s).

5 Characteristic stringency conditions are those which correspond to a combination of the temperature and of the saline concentration chosen approximately between 12 and 20°C under the T_m ("melting temperature") of the hybrid under study. Such molecules are synthesized and

10 may be labeled using conventional labeling methods used for molecular probes, or may be used as primers in amplification reactions. The sequences which exhibit at least 90% homology relative to a reference sequence also form part of the invention, as well as the

15 fragments of these sequences which have at least 20 nucleotides and preferably 30 contiguous nucleotides that are homologous with respect to a reference sequence. To reduce the proportion of natural or variant peptides, it is possible to envisage an

20 antisense and/or ribozyme approach. Such an approach is widely described in the literature. Of course, such antisense molecules may constitute, as such, vectors. It is also possible to use vectors which comprise a nucleic acid sequence which encodes an antisense.

25

The present invention relates to a biological material for the preparation of pharmaceutical compositions for treating mammals suffering from a degenerative and/or neurological and/or autoimmune disease, such as

30 multiple sclerosis, said composition comprising at least one nucleic acid sequence containing at least one gene of therapeutic interest and elements ensuring the expression of said gene *in vivo* in target cells intended to be genetically modified by said nucleic

35 sequence.

These nucleic acid sequences and/or vectors (antisense or encoding a protein or a fragment of a protein) make it possible to target the cells in which the peptide is

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expressed, such as macrophage cells: (i) either by the use of a targeting molecule introduced on the vector, (ii) or by the use of a particular property of these cells.

5

Use of vectors comprising a gene of therapeutic interest corresponding to the genes for the proteins of interest identified in the present invention.

10 The present invention relates to a biological material for the preparation of pharmaceutical compositions for preventing and treating degenerative and/or neurological and/or autoimmune diseases, such as multiple sclerosis, the composition comprising a
15 nucleic acid sequence comprising a gene of therapeutic interest and elements for expressing said gene of interest. The genes may be nonmutated or mutated. They may also consist of nucleic acids modified such that it is not possible for them to integrate into the genome
20 of the target cell, or of nucleic acids stabilized with the aid of agents, such as spermine.

Such a gene of therapeutic interest encodes in particular:

25

(i) either at least one protein chosen from the proteins identified in the present invention (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the fragments of said sequences belonging to the same
30 family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID
35 No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, or their fragment(s),

(ii) or at least all or part of a polyclonal or monoclonal antibody capable of binding to at least one protein or a protein fragment chosen from the proteins identified in the present invention (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29. This may include in particular a native transmembrane antibody, or a fragment or derivative of such an antibody, as long as said antibody, antibody fragment or derivative is expressed at the surface of the genetically modified target cell of the mammal and is capable of binding to a polypeptide present at the surface of a cytotoxic effector cell or of a helper T lymphocyte involved in the process for activating such a cell,

(iii) or at least one molecule inhibiting at least one protein or its fragments, said protein being chosen from the proteins identified (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29; the proteins

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inhibiting the function and/or the metabolism and/or the binding of the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29,

(iv) or at least one ligand or any portion of a ligand capable of binding to at least one protein or one protein fragment chosen from the proteins identified (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, and/or of inhibiting its function.

More particularly, the expression antibody fragment is understood to mean the F(ab)₂, Fab', Fab, sFv fragments (Blazar et al., 1997, Journal of Immunology 159: 5821-5833; Bird et al., 1988 Science 242: 423-426) of a native antibody and the expression derivative is understood to mean, for example, a chimeric derivative of such an antibody (see for example the chimeras of the Mouse/Human anti-CD3 antibodies in Arakawa et al.,

1996 J Biochem 120: 657-662 or the immunotoxins such as sFv-toxin by Chaudary et al 1989, Nature 339: 394-397). The expression transmembrane antibody is understood to mean an antibody in which at least the functional
5 region capable of recognizing and binding to its specific antigen is expressed at the surface of the target cells in order to allow said recognition and binding. More particularly, the antibodies according to the present invention consist of fusion polypeptides
10 comprising the amino acids defining said functional region and an amino acid sequence (transmembrane polypeptide) allowing anchoring within the membrane lipid double layer of the target cell or at the outer surface of this bilayer. The nucleic sequences encoding
15 numerous transmembrane polypeptides are described in the literature. According to a most advantageous case, the nucleic acid sequence encoding the antibody heavy chain is fused with the nucleic acid sequence encoding the said transmembrane polypeptide.

20

The expression elements ensuring the expression of said gene *in vivo* refers in particular to the elements necessary to ensure the expression of said gene after its transfer into a target cell. This includes in
25 particular promoter sequences and/or regulatory sequences which are efficient in said cell, and optionally the sequences required to allow expression at the surface of the target cells of said polypeptide. The promoter used may be a viral, ubiquitous or tissue-specific promoter or a synthetic promoter. By way of
30 example, there may be mentioned promoters such as the promoters of the viruses RSV (Rous Sarcoma Virus), MPSV, SV40 (Simian Virus), CMV (Cytomegalovirus) or of the vaccinia virus, the promoters of the gene encoding
35 muscle creatine kinase, actin. It is, in addition, possible to choose a promoter sequence specific for a given cell type, or activable under defined conditions. The literature provides a large amount of information relating to such promoter sequences.

Moreover, said nucleic acid may comprise at least two sequences, which are identical or different, exhibiting a transcriptional promoter activity and/or at least two
5 genes, which are identical or different, situated relative to each other contiguously, apart, in the same direction or in the opposite direction, provided that the transcriptional promoter function or the transcription of said genes is not affected.

10

Likewise, in this type of nucleic acid construct, it is possible to introduce "neutral" nucleic sequences or introns which do not adversely affect the transcription and are spliced before the translational step. Such
15 sequences and their uses are described in the literature (reference: PCT patent application WO 94/29471).

Said nucleic acid may also comprise sequences required
20 for intracellular transport, for replication and/or for integration, for transcription and/or translation. Such sequences are well known to persons skilled in the art.

Moreover, the nucleic acids which can be used according
25 to the present invention may also be nucleic acids modified such that it is not possible for them to integrate into the genome of the target cell or nucleic acids stabilized with the aid of agents, such as, for example, spermine, which, as such, have no effect on
30 the efficiency of the transfection.

According to one embodiment of the invention, the nucleic acid sequence is a naked RNA or DNA sequence, that is to say which is free of any compound
35 facilitating its introduction into cells (transfer of nucleic acid sequence). However, according to a second embodiment of the invention, to promote its introduction into the target cells and to obtain the genetically modified cells of the invention, this

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nucleic acid sequence may be in the form of a "vector" and more particularly in the form of a viral vector, such as, for example, an adenoviral vector, a retroviral vector, a vector derived from a poxvirus, in particular derived from the vaccinia virus or from the Modified Virus Ankara (MVA) or from a nonviral vector such as, for example, a vector consisting of at least one said nucleic acid sequence complexed or conjugated with at least one carrier molecular substance selected from the group consisting of a cationic amphiphile, in particular a cationic lipid, a cationic or neutral polymer, a practical polar compound chosen in particular from propylene glycol, polyethylene glycol, glycerol, ethanol, 1-methyl-2-pyrrolidone or their derivatives, and an aprotic polar compound chosen in particular from dimethyl sulfoxide (DMSO), diethyl sulfoxide, di-n-propyl sulfoxide, dimethyl sulfone, sulfolane, dimethylformamide, dimethylacetamide, tetramethylurea, acetonitrile or their derivatives. The literature provides a large number of examples of such viral and nonviral vectors.

Such vectors may in addition and preferably comprise targeting elements which can make it possible to direct the transfer of a nucleic acid sequence toward certain cell types or certain particular tissues such as cytotoxic cells and antigen-presenting cells). They can also make it possible to direct the transfer of an active substance toward certain preferred intracellular compartments such as the nucleus, the mitochondria or the peroxisomes, for example. This may also include elements facilitating penetration into the cell or the lysis of intracellular compartments. Such targeting elements are widely described in the literature. This may include, for example, all or part of lectins, peptides, in particular the peptide JTS-1 (see PCT patent application WO 94/40958), oligonucleotides, lipids, hormones, vitamins, antigens, antibodies, ligands specific to membrane receptors, ligands capable

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of acting with an antiligand, fusogenic peptides, nuclear localization peptides or a composition of such compounds.

5 Use of cells transformed *in vivo* after injection of vectors containing at least one gene of therapeutic interest defined from the proteins of interest identified in the present invention (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the
10 fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5
15 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29.

20

The present invention relates to a biological material for the preparation of pharmaceutical compositions for preventing and treating mammals suffering from degenerative and/or neurological and/or autoimmune
25 diseases, preferably multiple sclerosis, the composition comprising at least one vector containing a therapeutic gene as described below, capable of being introduced into a target cell *in vivo* and of expressing the gene of therapeutic interest *in vivo*. The advantage
30 of this invention consists in the possibility of maintaining long term a basal level of molecules expressed in the patient treated. Vectors or nucleic acids encoding genes of therapeutic interest are injected. These vectors and nucleic acids should be
35 transported up to the target cells and transfect these cells in which they have to be expressed *in vivo*.

The invention relates to the expression *in vivo* of nucleotide sequences and/or vectors as designated in

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the preceding paragraph, that is to say sequences corresponding to genes of therapeutic interest encoding in particular:

- 5 (i) either at least one protein chosen from the proteins identified in the present invention (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor
10 of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit
15 at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, or their fragment(s),
- 20 (i) or at least all or part of a polyclonal or monoclonal antibody capable of binding to at least one protein chosen from the proteins identified in the present invention (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the fragments of said
25 sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID
30 No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29. This may
35 include a native transmembrane antibody, or a fragment or derivative of such an antibody, as long as said antibody or antibody fragment or derivative is expressed at the surface of the genetically modified target mammalian cell and in that said antibody is

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capable of binding to a polypeptide present at the surface of a cytotoxic effector cell or of a helper T lymphocyte and involved in the process of activating such a cell. This may include antibody fragments
 5 expressed by cells capable of secreting said antibodies in the bloodstream of a mammal or patient carrying the cells genetically modified by the gene encoding the antibody,

10 (ii) or at least one molecule inhibiting at least one protein chosen from the proteins identified (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor
 15 of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit
 20 at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29; protein inhibiting the function and/or metabolism and/or binding of the proteins SEQ ID No. 2, 4, 8, 9, 17, 24
 25 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example
 30 SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of
 35 the peptide sequences SEQ ID No. 1 to 29,

(iii) or at least one ligand or any portion of the ligand capable of binding to at least one protein chosen from the proteins identified (SEQ ID No. 2, 4,

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8, 9, 17, 24) and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, and/or of inhibiting its function.

According to a particular embodiment, this includes using gene therapy so as to direct the immune response against the target protein, peptide or molecule of interest, that is to say against any protein chosen from the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, their fragment(s) and/or against any molecule inhibiting the function and/or expression and/or metabolism of said proteins of interest, and/or ligands of said proteins such as, for example, the receptors. For that, it is evident that the cells to be targeted for the transformation with a vector are cells belonging to the immune system, either lymphocyte-type cells (CD4/CD8), or antigen-presenting cells (dendritic cells, macrophages and the like).

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According to a particular embodiment, the antigen-presenting cells (APC) are genetically modified, in particular *in vivo*. APCs such as macrophages, dendritic cells, microgliocytes and astrocytes play a role in
5 initiating the immune response. They are the first cellular components which capture the antigen, prepare it in the cell and express the transmembrane MHC I and MHC II molecules involved in presenting the immunogen to the CD4+ and CD8+ T cells, they produce specific
10 secondary proteins which participate in activating the T cells (Debrick et al., 1991, J. Immunol 147: 2846; Reis et al., 1993, J Ep Med 178: 509; Kovacsovics-bankowski et al., 1993, PNAS 90: 4942; Kovacsovics-bankowski et al., 1995 Science 267: 243; Svensson et
15 al., 1997, J Immunol 158: 4229; Norbury et al., 1997, Eur J Immunol 27: 280). For a vaccination, it may be advantageous to have a gene therapy system which can target the gene transfer into such APC cells, that is to say a gene which encodes a polypeptide which can,
20 after its intracellular production and its "processing", be presented to the CD8+ and/or CD4+ cells by the molecules of the MHC I and MHC II complexes, respectively, at the surface of these cells.

25 It is chosen to express at the surface of the APC cells *in vivo* all or part of an antibody and/or of a ligand such as, for example, a receptor, capable of reacting with the target protein or peptide chosen from the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide
30 sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID
35 No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide

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sequences SEQ ID No. 1 to 29. Such cells will then specifically phagocytose said protein or said peptide, the "processor" so that fragments of this peptide are present at the surface of the antigen-presenting cells.

5

The literature provides a large number of examples of genes encoding antibodies capable of reacting with polypeptides or receptors. It is within the capability of persons skilled in the art to obtain the nucleic acid sequences encoding such antibodies. There may be mentioned, for example, the genes encoding the light and heavy chains of the antibody YTH 12.5 (anti-CD3) (Routledge et al. 1991, Eur J Immunol 21: 2717-2725), of the anti-CD3 according to Arakawa et al; 1996, J. Biochem. 120: 657-662. The nucleic acid sequences of such antibodies are easily identifiable from the databases commonly used by persons skilled in the art. It is also possible, starting with hybridomas available from ATCC, to clone the nucleic acid sequences encoding the heavy and/or light chains of these various antibodies by amplification methods such as RT-PCR with the aid of specific oligonucleotides or techniques using cDNA libraries (Maniatis et al., 1982, Molecular cloning. A laboratory manual CSH Laboratory, Cold Spring Harbor, New York). The sequences thus cloned are then available for their cloning into vectors. According to a preferred case of the invention, the nucleic acid sequence encoding the heavy chain of the antibody is fused by homologous recombination with the nucleic acid sequence encoding a transmembrane polypeptide such as the rabies glycoprotein or gp160 (Polydefkis et al., 1990, J Exp Med 171: 875-887). These molecular biology techniques have been fully described.

35

It is chosen to express at the surface of the APC cells *in vivo* immunogenic fragments corresponding to at least one proteins chosen from the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments

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of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29. For that, it is possible to choose to cause the vector to express either the full-length polypeptide or, preferably, polypeptides selected to react with specific ligands and/or receptors. The immunogenic peptide encoded by the polynucleotide introduced into the cell of the vertebrate *in vivo* may be produced and/or secreted, made ready and then presented to an antigen-presenting cell (APC) in the context of the molecules of the MHC. The APCs thus transferred *in vivo* induce an immune response directed against the immunogen expressed *in vivo*. The APCs possess different mechanisms for capturing the antigens: (a) capture of the antigens by membrane receptors such as the receptors for immunoglobulins (Fc) or for the complement which are available at the surface of the granulocytes, monocytes or macrophages allowing efficient delivery of the antigen into the intracellular compartments after phagocytosis mediated by the receptors. (b) entry into the APCs by pinocytosis in fluid phase, involving various mechanisms: micropinocytosis, that is to say the capture of small vesicles (0.1 μm) by the clathrin-coated pits, and macropinocytosis, that is to say the capture of larger vesicles (with a size varying graft 0.5 μm and about 6 μm) (Sallusto et al. 1995, J Exp Med 182: 389-400). While micropinocytosis constitutively exists in all cells, macropinocytosis is limited to cellular types such as, for example, the macrophages, dendritic cells, astrocytes, epithelial cells stimulated by growth factors (Racoosin et al., J Cell

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Sci 1992, 102: 867-880). In this invention, the expression cells capable of macropinocytosis is understood to mean the cells which can carry out the events described above and the cells which can capture
5 macromolecules preferably between 0.5 μ m and about 6 μ m in the cytoplasm.

According to a particular embodiment, the cytotoxic effector cells or the helper T lymphocytes are
10 genetically modified in particular *in vivo* so that they express at their surface a polypeptide corresponding to the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from
15 Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the
20 peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, ligands for said proteins, which are naturally not expressed by these
25 cells and which are capable of inducing the process of activation of such cells, by introducing into these cells nucleic acid sequences containing the gene encoding such a polypeptide. In accordance with the present invention, it is also possible to select a
30 nucleic acid sequence containing a gene of therapeutic interest encoding all or part of an antibody directed against a protein chosen from the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor
35 of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID

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No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, capable of
 5 being expressed at the surface of the target cells of the patient to be treated, said antibody being capable of binding to a polypeptide which is naturally not expressed by these cytotoxic effector cells or helper T lymphocytes.

10

The expression cytotoxic effector cells is understood to designate the macrophages, astrocytes, cytotoxic T lymphocytes (CTL) and killer (NK) cells as well as their derivatives such as, for example, LAKs (Versteeg
 15 1992 Immunology today 13: 244-247; Brittende et al 1996, Cancer 77: 1226-1243). The expression "helper T lymphocytes" is understood to designate in particular the CD4 cells which allow, after activation, the secretion of factors for activating the effector cells
 20 of the immune response. The polypeptides, and in particular the receptors expressed at the surface of these cells and which are involved in the activation of such cells, constitute in particular all or part of the TCR complex or CD3, all or part of the CD8, CD4, CD28, LFA-1, 4-1BB (Melero et al., 1998, Eur J Immunol 28:
 25 1116-1121), CD47, CD2, CD1, CD9, CD45, CD30 and CD40 complexes, all or part of the cytokine receptors (Finke et al., 1998, Gene therapy 5: 31-39), such as IL-7, IL-4, IL-2, IL-15 or GM-CSF, all or part of the
 30 receptor complex for the NK cells such as for example NKAR, Nkp46, and the like; (Kawano et al., 1998 Immunology 95: 5690-5693; Pessino et al., 1998 J Exp Med 188: 953-960), Nkp44, all or part of the macrophage receptors such as for example the Fc receptor (Deo et
 35 al., 1997, Immunology Today 18: 127-135).

Numerous tools have been developed for introducing various heterologous genes and/or vectors into cells, in particular mammalian cells. These techniques may be

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divided into two categories: the first category involves physical techniques such as microinjection, electroporation or particle bombardment. The second category is based on the use of molecular and cell biology techniques with which the gene is transferred with a biological or synthetic vector which facilitates the introduction of the material into the cell in vivo. Nowadays, the most efficient vectors are the viral, in particular adenoviral and retroviral, vectors. These viruses possess natural properties for crossing the plasma membranes, avoiding degradation of their genetic material and introducing their genome into the nucleus of the cell. These viruses have been widely studied and some are already experimentally used in human applications in vaccination, immunotherapy, or to compensate for genetic deficiencies. However, this viral approach has limitations, in particular due to the restricted cloning capacity in these viral genomes, the risk of disseminating the viral particles produced in the body and the environment, the risk of artefactual mutagenesis by insertion into the host cell in the case of retroviruses, and the possibility of inducing a high inflammatory immune response in vivo during the treatment, which limits the number of injections possible (McCoy et al. 1995, Human Gene Therapy 6: 1553-1560; Yang et al., 1996 Immunity 1: 433-422). Other alternative systems to these viral vectors exist. The use of nonviral methods such as, for example, coprecipitation with calcium phosphate, the use of receptors which mimic the viral systems (for a summary see Cotten and Wagner 1993, Current Opinion in Biotechnology, 4: 705-710), or the use of polymers such as polyamidoamines (Haensler and Szoka 1993, Bioconjugate Chem 4: 372-379). Other nonviral techniques are based on the use of liposomes whose efficiency for the introduction of biological macromolecules such as DNA, RNA, proteins or active pharmaceutical substances has been widely described in the scientific literature. In this domain, teams have

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proposed the use of cationic lipids having a high affinity for the cell membranes and/or nucleic acids. Indeed, it has been shown that a nucleic acid molecule itself could cross the plasma membrane of some cells
5 *in vivo* (WO 90/11092), the efficiency depending in particular on the polyanionic nature of the nucleic acid. Since 1989 (Felgner et al., Nature 337: 387-388), cationic lipids have been proposed to facilitate the introduction of large anionic molecules, which
10 neutralizes the negative charges on these molecules and promotes their introduction into the cells. Various teams have developed such cationic lipids: DOTMA (Felgner et al., 1987, PNAS 84: 7413-7417), DOGS or TransfectamTM (Behr et al., 1989, PNAS 86: 6982-6986),
15 DMRIE and DORIE (Felgner et al., 1993 methods 5: 67-75), DC-CHOL (Gao and Huang 1991, BBRC 179: 280-285), DOTAPTM (McLachlan et al., 1995, Gene therapy 2: 674-622) or LipofectamineTM, and the other molecules described in patents WO9116024, WO9514651, WO9405624.
20 Other groups have developed cationic polymers which facilitate the transfer of macromolecules, in particular anionic macromolecules, into cells. Patent WO95/24221 describes the use of dendritic polymers, the document WO96/02655 describes the use of
25 polyethyleneimine or polypropyleneimine and the documents US-A-5595897 and FR 2719316, the use of polylysine conjugates.

Given that it is desired to obtain *in vivo* a
30 transformation targeted toward a given cell type, it is evident that the vector used should be able to be "targeted" itself, as described above.

Use of cells transformed *in vitro* or *ex vivo* with
35 vectors containing a gene of therapeutic interest defined in relation to the proteins of interest identified in the present invention (SEQ ID No. 2, 4, 8, 9, 17, 24) and the peptide sequences or the fragments of said sequences belonging to the same

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family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29.

10

The present invention relates to a biological material for the preparation of pharmaceutical compositions for preventing and treating degenerative and/or neurological and/or autoimmune diseases, preferably multiple sclerosis, the composition comprising at least one cell, in particular a cell not naturally producing antibodies, in a form allowing their administration into the body of a mammal, human or animal, as well as optionally their prior culture, said cell being genetically modified *in vitro* by at least one nucleic acid sequence containing at least one gene encoding *in vivo*:

(i) at least one protein chosen from the proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B (for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29) and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29 and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98%

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identity with any one of the peptide sequences SEQ ID No. 1 to 29, and any fragment,

(ii) at least one peptide defined from the primary
5 sequence of at least one protein chosen from the
proteins SEQ ID No. 2, 4, 8, 9, 17, 24 and the peptide
sequences or the fragments of said sequences belonging
to the same family of proteins chosen from Perlecan,
the precursor of the retinol-binding plasma protein,
10 precursor of the ganglioside GM2 activator, calgranulin
B and saposin B (for example SEQ ID No. 1, SEQ ID
No. 3, SEQ ID No. 5 to 7, SEQ ID No. 10 to 16, SEQ ID
No. 18 to 23, SEQ ID No. 25 to 29) and the peptide
sequences which exhibit at least 70% identity,
15 preferably at least 80% identity and advantageously at
least 98% identity with any one of the peptide
sequences SEQ ID No. 1 to 29,

(iii) at least any molecule inhibiting the function
20 and/or binding and/or expression of these proteins,

(iv) at least one peptide derived from the primary
sequence of a protein chosen from the proteins SEQ ID
No. 2, 4, 8, 9, 17, 24 and the peptide sequences or the
25 fragments of said sequences belonging to the same
family of proteins chosen from Perlecan, the precursor
of the retinol-binding plasma protein, precursor of the
ganglioside GM2 activator, calgranulin B and saposin B
(for example SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5
30 to 7, SEQ ID No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID
No. 25 to 29) and the peptide sequences which exhibit
at least 70% identity, preferably at least 80% identity
and advantageously at least 98% identity with any one
of the peptide sequences SEQ ID No. 1 to 29, and
35 capable of binding to at least one glycoprotein of the
MHCI,

(v) at least any antibody and any portion of antibody
which are capable of binding to at least one protein

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chosen from the proteins SEQ ID No. 2, 4, 8, 9, 17, 24,
and the peptide sequences or the fragments of said
sequences belonging to the same family of proteins
chosen from Perlecan, the precursor of the retinol-
5 binding plasma protein, precursor of the ganglioside
GM2 activator, calgranulin B and saposin B (for example
SEQ ID No. 1, SEQ ID No. 3, SEQ ID No. 5 to 7, SEQ ID
No. 10 to 16, SEQ ID No. 18 to 23, SEQ ID No. 25 to 29)
and the peptide sequences which exhibit at least 70%
10 identity, preferably at least 80% identity and
advantageously at least 98% identity with any one of
the peptide sequences SEQ ID No. 1 to 29.

More particularly, said target cell is obtained either
15 from the mammal to be treated, or from a mammal other
than that to be treated. In the latter case, it should
be noted that said target cell will have undergone a
treatment making it compatible with the mammal to be
treated. The expression "mammal" is preferably
20 understood to mean a human mammal. These cells are
established as cell lines and are preferably MHCII+ or
MHCII+-inducible such as the lymphocytes, monocytes,
astrocytes and oligodendrocytes.

25 The invention also relates to the modified cells and to
a method for preparing a cell as described above,
characterized in that there is introduced into a
mammalian cell not naturally producing antibodies, by
any appropriate means, at least one nucleic acid
30 sequence containing at least one gene of therapeutic
interest and elements ensuring the expression of said
gene in said cell, said gene of therapeutic interest
containing a nucleic acid sequence encoding a molecule
or a molecule fragment *in vivo*, as described
35 immediately above. More particularly, it relates to
prokaryotic cells, yeast cells and animal cells, in
particular mammalian cells transformed with at least
one nucleotide sequence and/or one vector as described
above.

According to a particular embodiment, the cells (dendritic cells, macrophages, astrocytes, CD4+ T lymphocytes, CD8+ T lymphocytes, and the like) of the patient or allogenic cells are placed in contact with a purified preparation of the target polypeptide, the latter being internalized, made ready and presented at the cell surface associated with the MHCI and/or MHCII molecules and thus to induce a specific immune response against the peptide. The "activated" cells are then administered to the patient in whom they will induce an immune response specific for the antigens (a natural route is used for the immune response, but what the antigen-presenting cell is going to present is checked).

According to a particular embodiment, the antigen-presenting cells (dendritic cell, macrophage, astrocytes, and the like) are modified *in vitro* in order to express the antigens in the transformed cell which will associate with the MHCI and/or MHCII molecules and be presented at the surface of the cells to induce a perfectly targeted immune reaction in the patient in whom the modified cell is administered.

All the vaccine approaches are not always satisfactory and lead, for example, to limited immune reactions directed solely against immunodominant epitopes or against antigens exhibiting great variability. Likewise, the incorrect presentation of the antigens by the glycoproteins of the MHC system at the surface of the cells does not make it possible to develop in the treated patient a suitable anti-protein of interest immunity. To overcome these problems, some authors have proposed, in the context of such vaccine methods, to select the antigenic minimal fragments corresponding to the peptide portions capable of being specifically recognized by the cytotoxic T lymphocytes, expressing them in the cells so that they associate with the

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molecules of the MHCI and are presented at the surface of the cells in order to induce a perfectly targeted immune reaction in the treated patient (Toes et al. 1997, PNAS 94: 14660-14665). More particularly, it has
5 been shown that epitopes of very small sizes (varying from 7 to about 13 amino acids), which are expressed from minigenes introduced into a vaccinia virus, could induce a cellular type immunization. It has moreover been shown that several minigenes could be conjointly
10 expressed starting with the same vector (this particular construct is called "string of beads"). Such a construct has the advantage of inducing a synergistic CTL-type immune reaction (Whitton et al., 1993 J. of Virology 67: 348-352).

15

Protocol for bringing the cells and the antigenic fragment into contact:

The presentation of the antigenic fragments by the MHCI
20 molecules depends on an identified intracellular method (see Groettrup et al., 1996 Immunology Today 17: 429-435 for a review) in which very short antigenic peptides (about 7-13 amino acids) are produced by degradation of a more complex polypeptide against which
25 the final immune reaction will be directed. These short peptides are then combined with the MHCI or MHCII molecules to form a protein complex which is transported to the cell surface in order to present said peptides to the circulating cytotoxic T
30 lymphocytes or to the circulating helper T lymphocytes, respectively. It should be noted, in addition, that the specificity of the MHCI or MHCII molecules toward the antigenic peptides varies as a function of the MHCI or MHCII molecules (example for MHCI: HLA-A, HLA-B, and
35 the like) and the allele (example for MHCI: HLA-A2, HLA-A3, HLA-A11) which are considered. Within the same animal species, from one individual to another, there is great variability of the genes encoding the molecules of the MHC system (on this subject, see in

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particular George et al., 1995, Immunology Today 16: 209-212).

According to a particular embodiment, the cells, such
 5 as dendritic cells, macrophages, astrocytes, CD4+
 T lymphocytes, CD8+ T lymphocytes, are modified so as
 to express at their surface antibodies specific for the
 targeted peptide. The peptide is neutralized with the
 antibodies expressed at the surface of the cells. These
 10 cells are preferably immune cells, preferably from the
 patient, are preferably cytotoxic and modified to
 express all or part of an antibody specific for the
 target polypeptide.

15 Isolation of mononucleated cells from peripheral blood:

In 1968, Boyum described a rapid technique which makes
 it possible, by centrifugation of blood on a density
 gradient, to separate the mononucleated cells
 20 (lymphocytes and monocytes) with a good yield
 (theoretical yield 50%, that is to say 10^6 cells/ml of
 blood). 50 ml of peripheral blood sterilely collected
 in heparinized tubes are centrifuged for 20 minutes at
 150 g at 20°C. The cells recovered are diluted in two
 25 volumes of initial peripheral blood of sterile PBS.
 10 ml of this suspension are deposited on 3 ml of a
 Ficoll-Hypaque solution (medium for separation of the
 lymphocytes, Flow). After centrifuging for 20 minutes
 at 400 g and 20°C without decelerating braking, the
 30 mononucleated cells sediment at the PBS-Ficoll
 interface, as an opalescent dense layer, whereas
 practically all the red blood cells and the polynuclear
 cells sediment at the bottom of the tube. The mono-
 nucleated cells are recovered and washed with sterile
 35 PBS.

Internalization of the antigens by the antigen-
 presenting cells:

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Prior treatment of the antigen-presenting cells: the antigen-presenting cells are washed beforehand with PBS buffer containing 0.5% (w/v) BSA, then counted and they are then preincubated in the presence of various reduction inhibitors three times in PBS-0.5% BSA containing 10 μ M to 10 mM final of DTNB (5,5'-dithio-bis-2-nitrobenzoic acid) or NEM (N-ethylmaleimide). The subsequent stages of binding of antigens to the cell surface or of internalization of antigens are also carried out in the presence of various concentrations of inhibitors.

Protocol for internalization of the antigens by the antigen-presenting cells:

8 $\times 10^6$ cells are internalized in the presence of saturating quantity of proteins radiolabeled with iodine 125 (1 μ g) in microwells in 70 μ l. After incubating for one hour at 4°C, with stirring, the antigens are bound to the surface of the cells. The cell suspension is washed twice in PBS-BSA and the cellular pellets are taken up in 70 μ l of buffer and incubated at 37°C for various periods ranging up to 2 hours. Cells and supernatants are separated by centrifugation at 800 g for 5 minutes 4°C. For longer incubation periods, the preliminary stage of prebinding of the antigens to the surface of the cells is eliminated. The cells are diluted in RPMI-10% FCS medium in the presence of 20 mM Hepes, at 10^6 cells/ml. The cells are incubated in the presence of an excess of antigen for various periods at 37°C (1 μ g of molecules/ 5×10^7 monocyte/macrophage cells or 10^8 B-EBV cells).

All the therapeutic agents defined in the context of the present invention are used for preventing and/or treating a degenerative and/or neurological and/or autoimmune disease, such as multiple sclerosis, alone or in combination. They may also be used to evaluate their efficacy *in vitro* or *in vivo*.

Administration of therapeutic agents in humans:

The biological material according to the invention may
5 be administered *in vivo* in particular in injectable
form. It is also possible to envisage injection by the
epidermal, intravenous, intraarterial, intramuscular or
intracerebral route with a syringe or any other
equivalent means. According to another embodiment, by
10 oral administration or any other means perfectly known
to a person skilled in the art and applicable to the
present invention. The administration may take place as
a single dose or as a dose repeated once or several
times after a certain time interval. The most
15 appropriate route of administration and dosage vary as
a function of various parameters such as, for example,
the individual or the disease to be treated, the stage
and/or the progression of the disease, or alternatively
the nucleic acid and/or protein and/or peptide and/or
20 molecule and/or cell to be transferred or the target
organ/tissue.

To carry out the treatment of the mammal mentioned in
the present invention, it is possible to have
25 pharmaceutical compositions comprising a biological
material as described above, advantageously combined
with a pharmaceutically acceptable vehicle for
administration to humans or to animals. The use of such
carriers is described in the literature (see, for
30 example, Remington's Pharmaceutical Sciences 16th ed.
1980, Mack Publishing Co). This pharmaceutically
acceptable vehicle is preferably isotonic, hypotonic or
exhibits low hypertonicity and has a relatively low
ionic strength, such as for example a sucrose solution.
35 Moreover, said composition may contain solvents,
aqueous or partially aqueous vehicles such as sterile
water, free of pyrogenic agents and dispersion media
for example. The pH of these pharmaceutical

compositions is suitably adjusted and buffered according to conventional techniques.

Figures:

5

Figure 1 represents the amino acid sequence of the GM2AP protein, and the localization of the peptides, which is underlined, and which are used for the production of anti-GM2AP peptides antibodies.

10

Figure 2 represents the amino acid sequence of the MRP14 protein, and the localization of the peptides, which is underlined, and which are used for the production of anti-MRP14 peptides antibodies.

15

Figure 3 represents the amino acid sequence of the Saposin B protein, and the localization of the peptides, which is underlined, and which are used for the production of anti-Saposin B peptides antibodies.

20

Figure 4 represents the assay of the MRP8 protein (ng/ml - on the y-axis) in the urine of patients suffering from multiple sclerosis (MS), in the urine of patients suffering from other neurological diseases (OND) and in the urine of controls considered healthy (HC). n means the number of urine samples tested per category.

25

Figure 5 represents the assay of the MRP14 protein (ng/ml - on the y-axis) in the urine of patients suffering from multiple sclerosis (MS), in the urine of patients suffering from other neurological diseases (OND) and in the urine of controls considered healthy (HC). n means the number of urine samples tested per category.

35

Figure 6 represents the assay of the MRP8/14 protein (ng/ml - on the y-axis) in the urine of patients suffering from multiple sclerosis (MS), in the urine of

patients suffering from other neurological diseases (OND) and in the urine of controls considered healthy (HC). n means the number of urine samples tested per category.

5

Figure 7 represents the mean concentrations of the MRP8, MRP14 and MRP8/14 proteins (ng/ml - on the y-axis) in the urine of patients suffering from multiple sclerosis (MS), in the urine of patients suffering from other neurological diseases (OND) and in the urine of controls considered healthy (HC). n means the number of urine samples tested per category.

10

Figure 8 represents the assay of the GM2AP protein (ng/ml - on the y-axis) in the urine of patients suffering from multiple sclerosis (MS), in the urine of patients suffering from other neurological diseases (OND) and in the urine of controls considered healthy (HC). n means the number of urine samples tested per category. MS means multiple sclerosis, OND means other neurological diseases and Healthy means samples from controls supposed healthy (HC).

15

20

Figure 9 represents the assay of the Saposin B protein ($\mu\text{g/ml}$ - on the y-axis) in the urine of patients suffering from multiple sclerosis (MS), in the urine of patients suffering from other neurological diseases (OND) and in the urine of controls considered healthy (HC). n means the number of urine samples tested per category. MS means multiple sclerosis, OND means other neurological diseases and Healthy means samples from controls supposed healthy (HC).

25

30

Figure 10 represents the codetection of the Saposin B ($\mu\text{g/ml}$ - on the y-axis) and GM2AP (ng/ml - on the x-axis) proteins in urine samples from MS patients, controls supposed healthy and patients suffering from other neurological diseases and the correlation observed between the levels of the two proteins.

35

Figure 11 represents: figure 11A, the assay of the GM2AP protein in ng/ml in the urine of an MS patient in progressive remittent form (light-colored curve) and the gliotoxicity as a percentage of dead cells estimated by the MTT test (dark-colored curve); figure 11B, the assay of the Saposin B protein in $\mu\text{g/ml}$ in the urine of an MS patient in progressive remittent form (light-colored curve) and the gliotoxicity as a percentage of dead cells estimated by the MTT test (dark-colored curve).

Figure 12 represents the product of the concentrations of the GM2AP and saposin B proteins in $\text{ng}\times\mu\text{g/ml}^2$ in the urine of an MS patient in progressive remittent form (light-colored curve) and the gliotoxicity as a percentage of dead cells estimated by the MTT test (dark-colored curve).

Figure 13 represents: figure 13A, the assay of the GM2AP protein in ng/ml in the urine of an MS patient in progressive remittent form (light-colored curve) and the gliotoxicity as a percentage of dead cells estimated by the MTT test (dark-colored curve); figure 13B, the assay of the Saposin B protein in $\mu\text{g/ml}$ in the urine of an MS patient in progressive form (light-colored curve) and the gliotoxicity as a percentage of dead cells estimated by the MTT test (dark-colored curve).

Figure 14 represents the product of the concentrations of the GM2AP and saposin B proteins in $\text{ng}\times\mu\text{g/ml}^2$ in the urine of an MS patient in progressive form (light-colored curve) and the gliotoxicity as a percentage of dead cells estimated by the MTT test (dark-colored curve).

Figure 15 represents the correlation between the concentrations of GM2AP in ng/ml (x-axis) and

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gliotoxicity as a percentage of dead cells estimated by the MTT test (y-axis) determined in the urine of MS patients and of controls.

5 Figure 16 represents the correlation between the concentrations of Saposin B in $\mu\text{g/ml}$ (x-axis) and gliotoxicity as a percentage of dead cells estimated by the MTT test (y-axis) determined in the urine of MS patients and of controls.

10

Figure 17 represents the correlation between the product of the concentrations of GM2AP and Saposin B in $\text{ng}\times\mu\text{g/ml}^2$ (x-axis) and gliotoxicity as a percentage of dead cells estimated by the MTT test (y-axis) determined in the urine of MS patients and of controls.

15

Figure 18 represents the correlation between the concentrations of GM2AP (ng/ml - on the left-hand y-axis), the concentrations of Saposin B ($\mu\text{g/ml}$ - right-hand y-axis) and the gliotoxicity as a percentage of dead cells estimated by the MTT test (x-axis). Two estimated correlation straight lines are represented on the graph. The lines in bold relate to the concentrations of saposin B; the lines in light black relate to the concentrations of GM2AP.

25

Examples:

Example 1: Collecting and pooling of urines

30

Urine samples of different volumes were collected from healthy individuals (MS-negative) having a priori no neurological or autoimmune disease. The toxic activity of each sample toward murine astrocyte cells was tested *in vitro* using the MTT test. In total, a pool of 20 liters of urine was formed (MS-negative pool). In parallel, urine samples of different volumes were collected from individuals suffering from multiple sclerosis (MS-positive) at various stages of the

35

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disease. The toxic activity of each sample toward murine astrocyte cells was tested *in vitro* using the MTT test. In total, a pool of 80 liters of urine was formed (MS-positive pool).

5

Example 2: Purification of the urinary proteins

The pools of MS-positive and MS-negative urine, collected and tested according to example 1, were
10 purified in order to obtain a high protein concentration and to remove the high molecular weight proteins as far as possible.

Precipitation: precipitations with ammonium sulfate
15 (Prolabo - ref. 21 333 365) were carried out on the pools of MS-positive and MS-negative urine. The percentage of 60% saturated ammonium sulfate per 40% of urine, that is 390 grams of ammonium sulfate per liter of urine, was used. Each pool was distributed into
20 fractions of 1.8 liters in 2-liter bottles in order to improve the precipitation. The precipitation was carried out for 2 x 8 hours, at room temperature, with gentle stirring. After centrifugation of the pools of urine at 3 000 rpm for 10 min, at a temperature of
25 10°C, the pellet obtained is taken up in 20 mM Tris buffer containing 1 mM CaCl₂ and 0.25 M urea. The mixture was then centrifuged at 3 000 rpm for 10 min. The supernatant contains the concentrated proteins. It is either used immediately for the next stage, or
30 frozen if the next stage cannot be performed continuously.

Ion-exchange chromatography: the solution containing the proteins was then passed over a DEAE fast Flow gel
35 (marketed by PHARMACIA). This stage is carried out at low pressure on a PHARMACIA column filled with gel. The buffers are brought to the column by a peristaltic pump which allows a uniform flow rate. The buffer for equilibrating the column is 20 mM Tris buffer, pH 7.

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The fraction corresponding to the precipitation supernatant and containing an excessively high quantity of salts is dialyzed against this buffer before depositing on the column. Elution with a salt gradient makes it possible to recover the proteins. The elution gradient is performed in steps of 100, 200, 300, 500 mM NaCl in the buffer for equilibrating the column. The elution fractions are tested by the MTT test and only the positive fractions, that is the fraction eluted at 200 Mm NaCl, will be preserved. These fractions may be immediately treated or stored in the freeze-dried state.

Purification: steric exclusion chromatography based on the difference in size and shape of the proteins to be eluted was used. The fraction corresponding to the 200 mM NaCl elution is deposited on the column. During the elution, the proteins of low molecular mass are retained and therefore eluted later than the large molecules. The purifications were carried out on HPLC with a TosoHaas TSK Prep G 3000 SW column having a diameter of 21.5 mm and a length of 300 mm, the molecular mass exclusion limit is 500 000 daltons. The elution buffer used contains 100 mM phosphate, 100 mM sodium sulfate, at pH 6.8. The separation of the protein mixture was carried out in 60 min. Only the fraction corresponding to a mass of 15-20 000 daltons was preserved. This fraction is dialyzed in 20 mM Tris buffer containing 0.2 mM CaCl_2 , pH 7.2, and then freeze-dried.

At each stage, only the fractions having a significant toxic activity were retained for the next stage. The toxic activity of the proteins was checked at each stage using the MTT test. Only the fractions having a significant toxic activity were retained for the additional purification stage described in example 3.

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Example 3: Additional purification of the urinary proteins by reverse phase chromatography

5 Pools of urine from MS patients (MS-positive pool) and from non-MS patients (MS-negative pool), obtained after purification according to example 2, were taken up in distilled water and then diluted with a 0.2% TFA/10% acetonitrile solution in order to obtain a final concentration of about 130 to 140 µg/ml.

10

The separation by C8 reverse phase HPLC was carried out on a Brownlee Aquapore column (trade name) marketed by the company Perkin Elmer (column characteristics: 300 angstroms/7 µm/(100×4.6) mm). Two separate columns
15 were used for the positive and negative pools respectively. The injections were carried out by multiple injections of 250 µl. The proteins were eluted with a linear gradient from 5% to 15% of buffer B over 5 min, and then from 15% to 100% of buffer B over
20 95 min, at a flow rate of 0.5 ml/min. The separation buffers A and B used are the buffer 0.1% TFA (Pierce No. 28904)/MilliQ water and the buffer 0.09% TFA/80% acetonitrile (Baker) respectively. The detection was carried out by measuring the UV absorbance at 205 and
25 280 nm. Fractions were collected in 1.5 ml and 0.5-1 ml fractions in the zone of interest. The fractions were frozen after collection in dry ice.

The fractions collected were then dried in a speed vac
30 and taken up in 100 µl of 0.1% TFA/30% acetonitrile, 20 µl of the fractions were transferred into 500 µl eppendorfs, dried and washed twice with 100 µl of MilliQ water and then dried again.

35 The toxic activity of the proteins contained in each fraction collected after elution was determined with the aid of the MTT test. Only fraction 21 exhibiting a significant toxic activity was retained. The number for this fraction corresponds to the order of elution as a

- 95 -

function of the elution conditions stated in this example.

Example 4: Analysis of the proteins obtained by HPLC
5 separation on SDS-TRICINE gel

The collection pool for fraction 21 obtained by HPLC, as described in example 3, and resulting from 20 injections of the MS-positive pool, was deposited on a
10 precast 16% SDS-TRICINE gel of 10 wells and 1 mm thick (marketed by the company Novex). The conditions for using the gel correspond to those recommended by the supplier. The sample is taken up in 75 μ l of 1 times concentrated sample buffer (SDS-TRICINE No. LC 1676,
15 1 ml two times concentrated + 50 μ l of β -mercapto-ethanol (Pierce) diluted 1/2 in water) and 25 μ l of the sample are deposited on the gel in three portions. The collection pool for fraction 21 obtained from 6 injections of the MS-negative pool was deposited on the
20 gel under the same conditions as described for the MS-positive pool. The migration on the two gels was carried out in parallel in the same migration tank (XCELL II NOVEX (trade name)) at a constant voltage of 125 mV for 2 hours. The tank is placed in a container
25 containing ice. The gels were stained directly after migration by zinc/imidazole staining (staining kit 161-0440 marketed by the company BIORAD) so as to obtain a reversible negative staining. The protein bands are translucent on an opaque base.

30

Example 5: Digestion of the gel bands with trypsin

All the protein bands visualized in the deposits of fraction 21 were cut out and subjected to proteolysis
35 with trypsin.

The gel bands are cut out with a scalpel into slices of 1 mm and transferred into eppendorf tubes. The eppendorfs are subjected to a centrifugation peak so as

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to cause the gel pieces to fall and, after centrifugation, 100 μ l of washing buffer (100 mM NH_4CO_3 /50% CH_3CN) are added to the gel pieces. After stirring for 30 min at room temperature, the
 5 supernatant is removed in fractions of 20 μ l and the washing step is repeated twice. The eppendorfs are dried for 5 min in speed vac. 20 μ g of trypsin (modified sequenal grade PROMEGA V5111) are taken up in 200 μ l of digestion buffer (5 mM TRIS, pH 8) and are
 10 dissolved for 30 min at room temperature, with intermittent stirring, and 20 to 30 μ l of resuspended trypsin are added to the gel pieces. The eppendorfs are centrifuged and stored in a hot room at 28°C overnight. After digestion, the gel bands may be used immediately
 15 for the measurements of mass or frozen for subsequent use.

Example 6: Chemical digestion of the gel bands with CNBR

20

In the event of a protein being resistant to enzymatic cleavages, in particular to the action of trypsin as described in example 5, the bands between 16 kD and 20 kD were treated with CNBR. The gel bands, already
 25 used for the digestions with trypsin, are dried for 5 to 10 min in speed vac.

A solution of CNBR (FLUKA) at 200 mg/ml was prepared in 70% formic acid (BAKER). 20 μ l of this solution were used to rehydrate the gel pieces. The reaction was
 30 carried out for 20 h at room temperature and in the dark. The peptides are extracted for 3 times 30 min with 100 μ l of 0.1% TFA/60% acetonitrile. The extraction solutions are combined and concentrated to 20 μ l. These samples are diluted 5-fold in 0.1% TFA/
 35 water. The separation conditions are those described for the peptides from the digestion with trypsin.

Example 7: Analysis by MALDI-TOF spectrometry

30 µl of extraction buffer (2% TFA/50% acetonitrile) are added to the samples. The eppendorfs to be analyzed
5 are subjected to a centrifugation of 5 min, and then to a sonication of 5 min, and finally to a centrifugation of 1 min.

On a stainless steel disk, 14 deposits of 0.5 µl of matrix (α-cyano-4-hydroxytranscinnamic acid at
10 saturation in acetone) are carried out. A fine uniform microcrystalline layer is obtained. 0.5 µl of a solution of 2% TFA/water are deposited on this sublayer on the 14 deposits, and then 0.5 µl of sample to be analyzed are added. 0.5 µl of a solution at saturation
15 with α-cyano-4-hydroxytranscinnamic acid in 50% acetonitrile/water is added to this drop thus formed. After drying at room temperature for 30 min, the crystalline deposits are washed with 2 µl of water which are immediately evacuated by a puff of air. All
20 the spectra are obtained on a BRUKER BIFLEX (trade mark) mass spectrometer equipped with a reflectron. The measurements (90 to 120 laser shots on the entire deposit) are accumulated in order to obtain a mass spectrum which is most representative of all the
25 peptides present in the matrix-sample sandwich. For each deposit, a calibration with the peptides from the autolysis of trypsin was made in order to be able to use a measurement accuracy of less than 100 ppm.

Searches in databanks were carried out in MS-FIT
30 PROTEINPROSPECTOR (<http://prospector.ucsf.edu>). The common parameters used in these searches are (1) database: NCBI nr, (2) a tolerance of 100-50 ppm, (3) the cysteins are not modified, (4) the methionines may be oxidized, (5) molecular weight range: 1 000-
35 100 000 Da, (6) up to 3 cleavage sites may be ignored.

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Example 8: N-terminal sequencing of the digestion peptides

5 (i) Extraction and separation by HPLC of the digestion peptides.

After the measurements of mass on the entire digestion, the rest of the peptides are extracted 3 times 30 min in a sonication bath with 0.1% TFA/60% acetonitrile. 10 The extraction solutions are combined and dried up to 20 µl in speed vac. After dilution in 80 µl of buffer A (0.1% TFA/water), the extractions of the gel bands, digested with trypsin, are injected onto a C18/MZ-Vydac/(125×1.6) mm/5 µm column. The elution of the 15 peptides is carried out at a flow rate of 150 µl/min, in a gradient ranging from 5% of buffer B (0.09% TFA/80% acetonitrile) to 40% of buffer B over 40 min, and then from 40% of buffer B to 100% of buffer B over 10 min. The detection is made by measuring the UV 20 absorbence at 205 nm. The collection of the peaks is carried out in 500 µl eppendorf tubes. The fractions are stored on ice and, for the band of 18-20 kD of the MS-positive pool 21, analyzed by MALDI-TOF mass spectrometry.

25

(ii) N-terminal sequencing

The fractions corresponding only to a single mass peak were analyzed by Edman degradation on a sequencer 30 (model 477A PERKIN ELMER/Applied Biosystems). The sequencing conditions are those described by the manufacturer. A microcartridge was used for depositing the samples and the PTH-amino acids are identified with an online HPLC system (model 120A PERKIN ELMER/Applied 35 Biosystems).

The deposition of the fraction to be sequenced is made in several depositions of 15 µl with intermediate dryings. The tube which contained the peptide is washed

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with 15 µl of 85% formic acid (BAKER). The amino acid sequences still correspond to the masses measured. The peptides, whose masses do not correspond to the principal protein identified, were sequenced as a priority. In this manner, it was possible to identify up to three proteins in a gel band.

Example 9: Results and discussion.

10 After reversed HPLC of the MS-negative control pool and of the MS-positive pool, the toxic activity of each elution fraction was determined using the MTT test. Only fraction 21 of the MS-positive pool exhibits a toxic activity *in vitro*. Fraction 21 of the MS-negative control pool exhibits no toxic activity. The toxic activity of fraction 21 of the MS-positive pool was confirmed *in vitro* by FACS, as described in patent application WO 98/11439 on murine astrocyte cells.

20 The protein content of fraction 21 of the MS-negative control pool and of the MS-positive pool was observed after separation on 16% SDS-TRICINE gel and staining of the gel with zinc/imidazole. Proteins of high apparent molecular weights were found in the two fractions. On the other hand, five different bands of low apparent molecular weights are only visible in fraction 21 of the MS-positive pool (bands 8, 14, 18 and 20 kD). To each band there corresponds at least one protein and variants of said proteins which have an apparent molecular weight close to that of the native protein. These variant sequences exhibit a percentage homology or identity with the native sequences of at least 70%, preferably of at least 80% and advantageously of at least 98%.

35

The proteins of interest of fraction 21 of the MS-positive pool were then analyzed by mass spectrometry and/or sequencing and searching for homology in the databanks. The results show the presence of five

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protein bands migrating between 22 and 5 kD in fraction 21 of the MS-positive pool and variants of said proteins.

5 These proteins are the C-terminal fragment of Perlecan, which starts at amino acid 3464 and ends at amino acid 3707 of the complete protein sequence, identified in the sequence identifier SEQ ID No. 2, the precursor of the retinol-binding plasma protein whose sequence is
10 given in SEQ ID No. 4, the precursor of the ganglioside GM2 activator identified in SEQ ID No. 8, calgranulin B identified in SEQ ID No. 17 and saposin B represented in SEQ ID No. 24. As described above, homologs or variants of said proteins were also identified by
15 sequencing. These homologous or variant protein sequences are the product of mutations in the genes encoding said proteins. By way of example, SEQ ID No. 9 exhibits 99% homology or identity with SEQ ID No. 8 of the precursor of the ganglioside GM2 activator and the
20 fragment of SEQ ID No. 9 which starts at amino acid 34 and ends at amino acid 202 exhibits 98.88% homology or identity with the fragment corresponding to the native protein identified in SEQ ID No. 8.

25 Example 10: Identification of the proteins in a urine sample

Urine samples from an MS-negative individual and from an MS-positive patient were collected. These urine
30 samples were purified according to the protocol described above. The final elution fractions 21 were analyzed separately by mass spectrometry. The mass profile of each fraction corresponding to each urine sample was compared with the mass profile obtained for
35 the proteins identified in the preceding examples. The results show that for the urine sample from the MS-positive patient, the masses correspond to the molecules (i) C-terminal fragment of Perlecan, (ii) precursor of the ganglioside GM2 activator protein,

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(iii) calgranulin B and (iv) saposin B identified above. On the other hand, none of these masses was identified in the mass profile obtained after analysis of the urine sample obtained from the MS-negative individual. The method described can be used as a diagnostic assay.

Example 11: Western blot assay

Western blottings were carried out on different fractions of crude or purified urine as described in example 2. Urine samples from healthy individuals and from patients suffering from multiple sclerosis are tested in parallel. The samples are deposited on an electrophoresis gel which makes it possible to separate the various proteins according to their molecular mass under the action of an electric field. The Western blottings are carried out after transferring the proteins from the gel onto a membrane. To visualize the transferred proteins, the membrane is saturated with saturation buffer and then incubated with an antibody directly labeled with alkaline phosphatase. The antibody used is an anticalgranulin antibody (mouse monoclonal antibody, clone CF 145 subtype IgG 2b marketed by the company Valbiotech: reference MAS 696p batch PC96G696). The substrate for the enzyme is 3,3'-(1,1'-biphenyl)-4,4'-diazonium dichloride and sodium 2-naphthalenylphosphate (marketed under the name β Naphthyl acid phosphate Sigma ref. N7375 and Tetrazotized δ -dianisidine D3502) is added for revealing the bands and visualizing the proteins linked to the antibody. A molecule with an apparent molecular mass of about 14 000 is revealed in the purified urines from patients suffering from MS, with a relatively intense signal. This protein corresponds to calgranulin B (apparent molecular mass: 14 kD). By contrast, no signal is observed from urine from healthy individuals. This observation confirms the presence of this protein specifically in the urines from patients suffering from

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MS and the use of a method of detection using an antibody recognizing the protein.

Example 12: Production of monoclonal antibodies

5

The production of monoclonal antibodies using ascites requires compatibility of the H-2 system between the hybridoma and the producing mouse. Twenty 6-week-old female Balb/c mice receive an injection of 0.5 ml of
10 Pristane (2,6,10,14-tetramethylpentadecane acid) in their peritoneal cavity, for the production of ascites (Porter et al., 1972). One week to 10 days later, 5×10^6 to 10×10^6 hybridomas, diluted in 0.5 ml of sterile buffer containing 0.145 M NaCl, 10 mM Na_2HPO_4 ,
15 2.7 mM KCl and 1.5 mM KH_2PO_4 at pH 7.4, are injected by the intraperitoneal route. The ascites appear one to two weeks later. The ascitic fluids present in the peritoneal cavity are then collected with a syringe after incision of the peritoneum. The fluid collected
20 is centrifuged at 3 000 g for 15 minutes at room temperature, filtered on gauze in order to remove the fat, and then buffered by adding 1/20th of its volume of 1M Tris-HCl at pH 8.0. This method makes it possible to obtain quantities of antibody 10 times higher than
25 those obtained by hybridoma culture.

The immunoglobulins present in the ascitic fluid are released by the salts (ammonium sulfate or sodium sulfate). The ascitic fluid is precipitated with 40% ammonium sulfate. After 20 minutes in the cold, the
30 solution is centrifuged for 15 minutes at 8 000 g at 4°C. The precipitate is washed and resuspended in the cold in a 40% ammonium sulfate solution and then centrifuged again. The new precipitate enriched with IgG is redissolved in PBS buffer and dialyzed overnight
35 against the 25 mM Tris-HCl buffer containing 150 mM NaCl, pH 7.4. In parallel, an agarose-Protein A (or protein G) column (marketed in the freeze-dried form, Pierce) is extensively washed with the 25 mM Tris-HCl buffer containing 150 mM NaCl, pH 7.4. The solution

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enriched with IgG is deposited on the column and then the column is washed. The IgGs retained by the column are eluted at acidic pH (200 mM glycine, pH 2.8). The eluted fractions are neutralized with one volume of 1M Tris-Base, pH 10.5. The immunoglobulin content of each fraction collected is quantified by reading the absorbance at 280 nm (ϵ 1%, 1 cm = 14.0, Prahl and Porter 1968). The rich fractions are pooled. The degree of purification of the pooled IgGs is analyzed by acrylamide gel electrophoresis in the presence of SDS. The purified IgGs are dialyzed overnight against the 25 mM Tris-HCl buffer containing 150 mM NaCl, pH 7.4, sterilely filtered, aliquoted and stored at -20°C . Their final concentration is determined by reading the absorbance at 280 nm or by micro-BCA assay. The immunogenic peptides designated by the references SEQ ID No. 58, SEQ ID No. 54, SEQ ID No. 55, SEQ ID No. 56, SEQ ID No. 57, SEQ ID No. 58, SEQ ID No. 59, and SEQ ID No. 65 were used for the production of monoclonal antibodies, according to the protocol described above. However, it is in the capability of persons skilled in the art to define other protocols for the production of monoclonal antibodies, for example using the techniques described by Köhler and Milstein and by Galfre G. et al. previously cited or techniques derived therefrom.

Production of recombinant proteins and of polyclonal and monoclonal antibodies

Recombinant proteins:

The recombinant proteins GM2AP (SEQ ID NO. 73) and Saposin B (SEQ ID NO. 74) used to produce the calibration series for this study were produced in a prokaryotic system and purified from the clones of these two proteins obtained in our laboratory using the methods and protocols well known to persons skilled in the art.

Anti-GM2AP or anti-Saposin B antibodies:

5 The anti-GM2AP or anti-Saposin B antibodies used to carry out the study were produced in our laboratory or generously given.

10 Anti-Saposin B and anti-GM2AP polyclonal antibodies (Li et al., Glycoconjugate, 1984) were used for the study (cf the examples below): they are called SAP84 and GM2AP84.

15 Anti-GM2AP or anti-Saposin B polyclonal antibodies were produced and purified in the laboratory using the protocols and methods well known to persons skilled in the art: 50 µg of prokaryotic GM2AP or Saposin B protein purchased were injected into rabbits on days D0, D28 and D56; two booster injections were carried out once per month for two consecutive months. The two
20 anti-GM2AP polyclonal antibodies and two anti-Saposin B polyclonal antibodies were thus obtained and their specificity toward the recombinant protein was verified by Western blotting and Elisa.

25 Anti-GM2AP or Saposin B peptides polyclonal antibodies were produced and purified in the laboratory using the protocols and methods well known to persons skilled in the art: 75 µg of GM2AP or Saposin B peptides defined, produced and coupled to KLH in our laboratory were
30 injected on days D0, D28 and D56; several boosts were thus carried out once per month for 5 consecutive months with injection of 75 µg each time. Four anti-GM2AP peptides polyclonal antibodies, four anti-Saposin B peptides polyclonal antibodies and four anti-MRP14
35 peptides rabbit polyclonal antibodies were obtained and their specificity toward the recombinant protein was verified by Western blotting and by Elisa. The sequence of the GM2AP, Saposin B and MRP14 peptides chosen are described in figures 1 to 3.

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The following were obtained:

- 5 - an antibody anti-mixture of two peptides of 13 and
15 amino acids of GM2AP: 189-190; an antibody anti-
peptide of 18 amino acids of GM2AP: 191-192 (cf.
figure 1),
- 10 - an antibody anti-mixture of two peptides of 13 and
19 amino acids of MRP14: 193; an antibody anti-peptide
of 17 amino acids of MRP14: 195-196 (cf. figure 2),
- 15 - an antibody anti-mixture of three peptides of 12, 15
and 15 amino acids of Saposin B: 74-75; another
antibody anti-mixture of 3 peptides of 12, 15 and 15
amino acids of Saposin B: 72-73 (cf. figure 3).

Anti-native fraction monoclonal antibodies were
produced and purified in the laboratory using the
20 protocols and methods well known to persons skilled in
the art. The "native fraction" corresponds to the
cytotoxic elution fraction obtained from the pool of
80 liters of urine from MS patients and after
purification. It is the last elution fraction which
25 contains the three proteins GM2AP, Saposin B, MRP14.
30 µg of this purification fraction were injected into
three mice on days D0, D14, D28 and the sample
collection was carried out on D38. After "screening"
and cell fusion, protocols known to persons skilled in
30 the art for establishing hybridomas and monoclonal
antibodies, the hybridomas were reinjected into the
mice and the ascitic fluid was recovered 10 days later.
The antibodies were purified on sepharose-Protein A
column and the specificity toward the fraction used for
35 the immunization was verified by Western blotting and
by Elisa. Thus, four monoclonal antibodies were
obtained: 191C1A7, 3D3F9, 18C8C5 and 7D12A8.

Example 13: Assay of the MRP14 proteins in the urines
by the ELISA technique

5 The MRP14, MRP8 proteins and the MRP8/14 heterocomplex
were assayed in human urines using (i) either an Elisa
assay technique according to the method known to
persons skilled in the art and using the anti-MRP
antibodies described in the preceding examples; (ii) or
the "MRP Enzyme Immunoassay" kit marketed by BMA
10 Biomedicals AG, Augst, Switzerland, using the
antibodies of the kit, the protocol being carried out
according to the leaflet in the kit.

Detection of MRP14 and MRP8/14 in urines

15

The assay was carried out using 17 urines of
individuals from the active population (HC), 27 urines
of patients suffering from multiple sclerosis (MS) and
7 urines of patients suffering from other neurological
20 diseases (OND).

- Figure 4 illustrates the levels of MRP8 assayed in
these urines: while the MRP8 concentration is
practically zero in the OND urines, there is no real
25 difference in distribution between the HC and MS
urines. It should be noted, however, that the
differences observed are practically negligible because
the concentrations assayed are extremely low.

30 - Figure 5 illustrates the levels of MRP14 assayed in
the same urines: while there are no real differences in
the distribution of the concentrations between the HC
and OND urines, the concentrations are higher in
certain MS urines.

35

- Figure 6 illustrates the levels of MRP8/14 hetero-
dimer assayed in the same urines: while there is no
real difference between the concentrations of the HC
and OND urines, higher concentrations are observed in

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certain MS urines, perhaps corresponding to a subpopulation of MS patients characterized by an activity of the disease. MRRP8/14 assayed in the urines is a marker for the activity of the MS disease
5 characterized by an inflammation peak).

- The recapitulative figure 7 confirms that there is no significant difference in MRP8 and MRP14 concentration between the HC, OND and MS urines, while a small
10 difference in MRP8/14 concentration is observed between these urines, this concentration being higher on average in the MS urines and being a marker for the activity of the disease (inflammation peak).

15 Example 14: ELISA protocols used for the assay of the GM2AP and Saposin B proteins

The GM2AP or Saposin B proteins were assayed in human urines using anti-GM2AP or anti-Saposin B? polyclonal
20 antibodies according to the Elisa protocol described by Gardas et al. (Glycoconjugate Journal 1, 37-42, 1984). The principal stages are briefly described below:

At each stage, the wells of a 96-well microplate are
25 filled with 200 μ l of the designated solution. The wells are first "coated" with a solution of GM2AP (prokaryotic recombinant protein) diluted to 50 ng/ml in a carbonate-bicarbonate buffer, pH 9.6. After incubating overnight at 4°C, the solution is removed
30 and the wells are washed four times with PBS buffer pH 7.4 containing 0.05% Tween-20 (PBS-Tween). The microplates thus coated are stored at 4°C for about 2 weeks.

35 The urine samples at three different dilutions (20x, 40x and 80x or other appropriate dilutions) are incubated with an appropriate dilution of the anti-GM2AP or anti-Saposin B rabbit polyclonal antibody overnight at 4°C. A standard series of dilutions of a

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recombinant protein ranging from 2.0 to 62.5 ng/ml is used to prepare the calibration series and are treated in the same manner. All the dilutions are made in PBS-Tween buffer containing 1 mg/ml of ovalbumin. Thus, 5 0.2 ml of each incubated solution is added to "coated" wells in duplicate and the plates are left for 2 hours at room temperature. The wells are then washed four times in PBS-Tween and again filled with a solution of anti-rabbit IgG goat antibodies coupled to peroxidase 10 and diluted about 1 200-fold. After incubating for 2 hours at room temperature, the wells are washed four times in PBS-Tween and again filled with the staining reagent. The staining reagent consists of 100 mg of 2,2'-azino-di-(3-ethylbenzothiazoline)sulfonic acid and 15 10 µl of 30% hydrogen peroxide for one hour at room temperature and the degree of staining of each microwell is estimated by reading the absorbance at 405 nm.

20 A standard curve is constructed by placing on the x-axis the concentration of GM2AP in the calibration series or of Saposin B with a logarithmic scale and on the y-axis the percentage absorbance with a linear scale. The percentage absorbance of the sample is the 25 absorbance ratio between the urine sample and the control which contains only the antiserum, without the soluble antigen.

A solution of recombinant protein GM2AP produced in a 30 prokaryotic system, and having a concentration of 3 mg/ml, is diluted in 50 mM carbonate buffer, pH 9.6, and 50 µl are added to each well of a 96-well microplate, that is 50 µl per well of a solution at 0.5 µg/ml. The plates thus prepared are incubated 35 overnight at room temperature. The anti-GM2AP polyclonal antibody produced in the laboratory (rabbit 79) was purified and diluted in PBS-0.05% Tween buffer in the presence of 10% horse serum. This solution is diluted 1/8 000. The solution is used to

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produce a calibration series with 8 series points covering concentrations from 0 to 500 ng/ml. A preincubation is carried out overnight at room temperature between 100 μ l of antibody and 100 μ l of
5 urine sample to be assayed or of recombinant GM2AP or Saposin B protein solution serving for the calibration series. After washing the microplate in PBS-Tween, 50 μ l of the incubation mixture are added per well, and then incubated for two hours at room temperature. The
10 microplate is again washed in PBS-Tween, and then 50 μ l of anti-rabbit IgG antibody coupled to peroxidase and diluted 1/5 000 are added to each microwell of the plate and incubated for two hours at room temperature. After further washings of the microplate, 100 μ l of OPD
15 are added to each well and incubated for 20 minutes at room temperature. The staining of each well, proportional to the concentration of GM2AP or of Saposin B recognized by the specific antibody used, is estimated by reading the absorbance.

20 A solution of recombinant protein GM2AP or Saposin B produced in a prokaryotic system, with a concentration of 3 mg/ml, is diluted in 50 mM carbonate buffer, pH 9.6, and 50 μ l are added to each well of a 96-well
25 microplate, that is 50 μ l per well of a solution at 1.5 μ g/ml. The plates thus prepared are incubated overnight at room temperature. The purified anti-GM2AP peptides polyclonal antibodies produced in the laboratory (rabbit 190 and rabbit 191) are used alone
30 or as a mixture, diluted 1/1 000 for each, in PBS-0.05% Tween buffer in the presence of 10% horse serum. The calibration series is produced using the prokaryotic recombinant protein GM2AP or Saposin B diluted so as to cover the concentration range 0 to 1 500 ng/ml with
35 8 points. 100 μ l of antibody (one antibody or the two together) are preincubated in the presence of 100 μ l of urine sample to be tested or of recombinant GM2AP or Saposin B solution, overnight at room temperature. After washing the microplate in PBS-Tween, 50 μ l of the

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incubation mixture are added per well and then incubated for two hours at room temperature. The microplate is again washed in PBS-Tween, and then 50 µl of anti-rabbit IgG antibody coupled to peroxidase, 5 diluted 1/5 000, are added to each microwell of the plate and incubated for two hours at room temperature. After washing the microplate, 100 µl of OPD are added to each well and incubated for 20 minutes at room temperature. The staining of each well, proportional to 10 the concentration of GM2AP or Saposin B recognized by the specific antibody used, is estimated by reading the absorbance.

15 Example 15: Assay of the GM2AP proteins in the urines

The GM2AP protein was assayed in the urines of 22 patients suffering from multiple sclerosis (MS), 5 patients suffering from other neurological diseases (OND) and 9 individuals chosen from the active 20 population and taken during a medical visit (healthy), according to the Elisa protocol described below, using anti-GM2AP polyclonal antibodies. The MS patients selected for this study are confirmed patients, that is to say with various stages and profiles of the disease, 25 and different treatments, and the like.

The results of the assay are presented in figure 8. Whereas only 0/5 OND urines and 2/9 so-called "Healthy" urines have a GM2AP concentration greater than 30 200 ng/ml, 10/22 (that is 45%) have a concentration greater than 200 ng/ml.

These results indicate that while the GM2AP protein is present in a very low concentration (<400 ng/ml) in the 35 urines of individuals from the active population, it is present in higher concentration in the urines of MS patients. However, 12 MS urines also exhibit low levels of GM2AP. Among these 12 patients, 10 are under treatment. The high urinary concentrations of GM2AP

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appear to be a marker for the MS pathology, and more precisely a marker for one stage or one form of the disease, for the activity of the disease, and is certainly influenced by any ongoing treatment. It should be noted that two individuals in the active population have high GM2AP concentrations (these two cases were voluntarily included in the study, because they both exhibited a gliotoxic activity in their urines unlike the other individuals of this same category). It is impossible to know if they are healthy individuals, or individuals suffering from a pathological condition, or individuals suffering from multiple sclerosis because the samples from the so-called "Healthy" individuals were collected anonymously, with no knowledge of their clinical file.

Higher urinary concentrations of GM2AP are detected in the urines of MS patients; a high concentration of GM2AP can then be a marker for the MS pathology, and more precisely for one form of the disease, for one stage of the disease, or for a period of activity, and may be influenced by any ongoing treatment. These high urinary concentrations of GM2AP may also have a predictive value for the onset of a worsening of the disease, or for a benign MS at the onset of a progression, and the like.

The absolute values of the GM2AP concentrations detected in the urines are dependent on the affinity and the specificity of the antibody used, but in general, the tendency between the three groups of individuals is preserved regardless of the antibody used.

Example 16: Assay of the Saposin B proteins in the urines

The Saposin B protein was detected in the same urine samples as those used to study the detection of GM2AP.

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The assays were carried out in parallel with those of GM2AP, in the same study, according to the Elisa protocol described below, using anti-Saposin B polyclonal antibodies.

5

The results of the Saposin B assay are presented in figure 9. 0/5 OND urines and 2/9 Healthy urines have a Saposin B concentration greater than 2 µg/ml, while 6/22 (that is 27%) exhibit a concentration greater than
10 2 µg/ml.

These results indicate that the Saposin B protein is present in each urine (so-called healthy population or so-called sick population) at significant concentrations, that is to say <2 µg/ml. These assay results
15 are compatible with those described in the literature. However, even if Saposin B is present in each urine, it appears to be present in a higher concentration in certain MS urines. This increase in Saposin B
20 concentration in the MS urines is perhaps masked by the basal concentration of this protein in the ordinary state. Thus, the high urinary concentrations of Saposin B appear to be a marker for the MS pathology, and more precisely a marker for one stage or one form
25 of the disease, or for the activity of the disease, and is certainly influenced by any ongoing treatment. The Saposin B assayed alone appears, however, to be a marker which discriminates for one form or for one activity of the disease slightly less than GM2AP. It
30 should again be noted that two individuals from the active population have high Saposin B concentrations and they are the same individuals who also had a high GM2AP concentration in their urine.

35 In conclusion, higher urinary concentrations of Saposin B are detected in the urines of MS patients; a high Saposin B concentration can therefore be a marker for the MS pathology, and more precisely for one form of the disease, for one stage of the disease, or for a

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period of activity, and may be influenced by any ongoing treatment. These high urinary GM2AP concentrations may also have a predictive value for an onset of a worsening of the disease, or for a benign MS at the beginning of a progression, and the like. However, in general, the high Saposin B concentrations alone appear to be markers which are less discriminatory than high GM2AP concentrations alone.

10 The absolute values of the Saposin B concentrations detected in the urines are dependent on the affinity and specificity of the antibody used, but in general, the tendency between the three groups of individuals is preserved regardless of the antibody used.

15

Example 17: Coassay of the GM2AP and Saposin B proteins in the urines

Figure 10 presents the GM2AP concentrations assayed in the urine samples described in figure 5 relative to the Saposin B concentration assayed in these same samples and described in figure 6. The MS samples (dark diamonds) and the OND and "Healthy" samples (white diamonds) are presented on this graph.

25

On this graph, it appears clearly that:

- the higher the GM2AP concentration in the urines, the higher the Saposin B concentration. (We have shown that it is not a general case with other proteins and that it does not indicate a renal disturbance, with the assay of creatinine in parallel for each of the samples tested);

35 - the high GM2AP and Saposin B concentrations are characteristic of the MS samples (with the exception of two urines from the active population, mentioned above). These joint high GM2AP and Saposin B concentrations are markers for the MS pathology, more

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precisely for a window of the disease (quadran on the right and at the top of the graph).

5 In conclusion, this analysis confirms that high urinary concentrations of GM2AP (>400 ng/ml) and of Saposin B (>2 µg/ml) are codetected in the urines of MS patients and may represent markers for the MS pathology, more precisely for one form of the disease, for one stage of the disease, or for a period of activity, and may be
10 influenced by any ongoing treatment. It is advantageous to assay the two proteins in parallel in each sample, and to consider the two concentrations.

15 Assay of GM2AP and Saposin B in the urine of two patients in the form of kinetics

MS patient No. 1 - Progressive remittent form

20 Urines of this patient were collected during the progression of his disease. The patient was hospitalized on D0 for an attack. He was subjected on D1 to a flash of corticoids and was then monitored over time from a clinical point of view (the flash provided clinical improvement). Figure 11 shows the profile for
25 the assay of GM2AP and of Saposin B in these urines during the progression, and figure 12 shows the profile of the product of the two GM2AP and Saposin B concentrations, indicating a codetection of high concentrations. The high GM2AP and Saposin B
30 concentrations at the time of the attack and hospitalization decrease gradually over time after the flash of corticoids up to 90 days.

MS Patient No. 2 - Progressive form

35

Urines of this patient were collected during the progression of his disease. The patient was hospitalized on D0 for an attack. He was subjected on D1 to a flash of Endoxan and was then monitored over

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time from a clinical point of view (the flash provided clinical improvement and at D60, signs of a worsening of the disease were observed). Figure 13 shows the profile for the assay of GM2AP and of Saposin B in these urines during the progression, and figure 14 shows the profile of the product of the two GM2AP and Saposin B concentrations, indicating a codetection of high concentrations. The high GM2AP and Saposin B concentrations at the time of the attack and hospitalization decrease gradually over time after the flash of Endoxan (also called cyclophosphamide) up to 23 days and appear to increase, becoming high at D60, thus showing a perfect correlation with the progression of the clinical signs.

15

These results confirm that:

- high concentrations of GM2AP and Saposin B in the urines are markers for the MS pathology, and in particular the codetection of high concentrations of the two proteins together (indicated by the product of the two concentrations);

- the high concentrations of GM2AP and Saposin B in the urines are markers for the activity of the disease (here during the attack) or are markers influenced by the immunosuppressive treatments such as corticoids and Endoxan which lower the concentrations.

30 This example illustrates the fact that these markers can be used, inter alia:

- to carry out a therapeutic monitoring of a patient and evaluate the therapeutic benefits of a treatment for a given patient; or

- to predict a worsening of the disease, predict an activity peak, and the like

- to decide on an anticipated therapeutic resumption based on the clinical signs

Example 18: Correlation between the detection of the MRP14, GM2AP and Saposin B proteins in the urines and the gliotoxicity measured in these urines

To verify a correlation between the presence of these proteins alone or in combination in the urines and the gliotoxicity of the urines, the concentrations of a protein of interest and the gliotoxicity of a sample of urines from patients suffering from multiple sclerosis (MS), from patients suffering from other neurological diseases (OND) and from individuals taken from the active population termed "Healthy" were assayed in parallel. Among the MS patients, patients are noted with various forms and stages of the disease, under treatment or otherwise, at various activities of the disease.

The MRP, GM2AP and Saposin B proteins were assayed in human urines according to the Elisa protocols described above. The assays analyzed in this example are those described in the preceding examples. Each urine sample analyzed in Elisa was analyzed by the MTT test to measure the gliotoxicity of each sample. The gliotoxicity is expressed as a percentage of dead cells (estimated by colorimetry using tetrazolium salts) of a murine astrocyte cell line (CLTT1.1) after 48 hours of incubation in the presence of centrifuged urine.

Figure 15 represents the GM2AP concentration as a function of the gliotoxicity of the urines determined by the MTT test.

22 MS urines (gray diamonds), 5 OND urines (black diamonds) and 9 so-called "Healthy" urines (black diamonds) were presented on the graph. They are the same urines which were studied in examples 15 and 16.

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It is observed that all the control urines (OND and Healthy) have low levels of GM2AP (<400 ng/ml) and a low gliotoxicity (<15%), with the exception of a Healthy control urine (already commented upon in
5 example 15) for which a high GM2AP concentration and gliotoxicity are observed.

The MS urines are divided into three subpopulations:

- 10 - urines with low GM2AP concentration (<400 ng/ml) and low gliotoxicity (<15%),
- urines with low GM2AP concentration (<400 ng/ml) and gliotoxicity (>15%), that is essentially 3 urines,
- 15 - urines at high GM2AP concentration (>400 ng/ml) and high gliotoxicity (>15%).

These three subpopulations perhaps indicate MS
20 subpopulations, that is to say different forms or stages of the disease, different activities of the disease, different therapeutic benefits, and the like.

However, it can be noted that all the urines having a
25 high GM2AP concentration also have a high gliotoxicity.

In conclusion, a correlation is observed between high urinary GM2AP concentration and gliotoxicity (all the urines with a high GM2AP concentration are gliotoxic
30 (10/10), and all the urines with a low GM2AP concentration are not gliotoxic (<15%), with the exception of 3 urines/12 MS). This indicates the involvement of the GM2AP protein in the mechanism of gliotoxicity, alone or in combination, in its natural
35 or modified form, but which is recognizable by an anti-GM2AP antibody. Furthermore, the codetection of a high GM2AP concentration in the urines and of a high gliotoxicity correlates with one subpopulation of patients suffering from MS.

Figure 16 represents the Saposin B concentration as a function of the gliotoxicity of the urines determined by the MTT test.

5

22 MS urines (gray diamonds), 5 OND urines (black diamonds) and 9 so-called "Healthy" urines (light gray diamonds) were presented on the graph. They are the same urines which were studied in examples 15 and 16.

10 It is observed that the richer the urines are in Saposin B, the more gliotoxic they are. There is a fairly clear correlation between the Saposin B concentration and the gliotoxicity of the urines.

15 In conclusion: a correlation is observed between high urinary Saposin B concentration and gliotoxicity. This indicates involvement of the Saposin B protein in the mechanism of gliotoxicity, alone or in combination, in its natural or modified form, but which is recognizable
20 by the anti-Saposin B antibody used for the assay.

Figure 17 represents the product of the GM2AP and Saposin B concentrations as a function of the gliotoxicity of the urines determined by the MTT test.

25

The 22 MS urines (gray diamonds), 5 OND urines (black diamonds) and 9 so-called "Healthy" urines (light gray diamonds) of examples 15 and 16 were presented in figure 17. The gliotoxicity of these urines is analyzed
30 according to the product of the GM2AP and Saposin B concentrations, that is to say according to the codetection of the two proteins in the urines. A correlation is very clearly observed between the product of the two GM2AP and Saposin B concentrations
35 and the gliotoxicity which is much higher than on considering only one protein. It is observed that 5/5 of the OND urines have a low product of GM2AP and Saposin B concentration and a low gliotoxicity; 8/9 "Healthy" urines have a low product of GM2AP and

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Saposin B concentration and/or a low gliotoxicity. On the other hand, essentially three subpopulations of MS urines are distinguished:

5 - urines at low GM2AP.Saposin B concentration and low gliotoxicity (<15%),

- urines at high GM2AP.Saposin B concentration and high gliotoxicity (>15%).

10

These two subpopulations perhaps indicate MS subpopulations, that is to say different forms or stages of the disease, different activities of the disease, different therapeutic benefits and the like.

15

However, it is very important to note that all the urines having a high GM2AP and Saposin B concentration, that is to say having simultaneously a high GM2AP and Saposin B concentration, also have a high gliotoxicity. The two subpopulations of MS patients are all the more marked and clear when the three markers are considered together: gliotoxicity, high GM2AP concentration and high Saposin B concentration. This is confirmed in figure 18.

20

25

In conclusion: a correlation is observed between high urinary GM2AP and Saposin B concentration and gliotoxicity. All the urines with a high GM2AP and Saposin B concentration are gliotoxic, and all the urines with a low GM2AP and Saposin B concentration are not gliotoxic (<15%), with the exception of 2 urines/22 MS. This indicates the involvement of the two proteins GM2AP and Saposin together or in combination in the mechanism of gliotoxicity, in their natural or modified form, but which is recognizable by

30

35

the anti-GM2AP and anti-Saposin B antibodies used for the assay. Furthermore, the codetection of a high urinary GM2AP and Saposin B concentration and of a high gliotoxicity correlates with a subpopulation of patients suffering from MS (stage, form, activity,

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monocytes and not in those of the control monocytes, on days D6 and especially D9 of the culture; the proteins are not detected beyond this kinetic. It should be noted that the antibodies used for the assay can
5 recognize the physiological forms of the proteins, but also the complexed and/or modified forms.

It is therefore observed that the period D6-D9 during which the highest gliotoxicity is observed in the
10 supernatant is covered by the period D3-D15 during which a less differentiated production of the negative control for GM2A is observed in the cells with quantitative and qualitative fluctuations of its cellular expression (quantity of expression and
15 cellular localization).

Example 20: Immunohistological technique on brain sections in paraffin

20 The histological sections prepared in paraffin are made paraffin free in xylene and alcohol before undergoing a pretreatment intended to unmask the antigens; this pretreatment may correspond to (i) twice 5 minutes under microwave (750W) in the presence of a sodium
25 citrate, citric acid buffer, (ii) a treatment with acid by incubating for 15 minutes in a 1% periodic acid solution or by incubating for 5 minutes in a 99% formic acid solution. The endogenous peroxidases are then blocked by incubating the slides for 30 minutes in 1%
30 hydrogen peroxide, followed by extensive washing in water for 15 minutes. The background noise is blocked by incubating the slides for 30 minutes in the presence of PBS-0.03% Triton, 10% Donkey serum (for the polyclonal antibodies) or 10% Goat serum (for the
35 monoclonal antibodies). Labeling with the primary antibody is carried out by applying 100 to 200 µl of primary antibody solution per slide (0.5 to 5 µg/ml according to the titer) in PBS-0.03% Triton and then incubating for 2 hours at room temperature. The slides

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are then rinsed 3 times in PBS-Triton for 10 minutes. Secondary antibody labeling is carried out using biotinylated antibodies capable of binding specifically to the primary antibodies, for example anti-rabbit IgG or anti-mouse IgG antibodies diluted in PBS-0.03% Triton. The slides are washed and incubated in a solution for 2 hours (2 μ l streptavidin-biotin-peroxide complex, 1 600 μ l PBS-0.03% Triton). The slides are again washed before being revealed, protected from light, in buffer A and then rinsed with water before microscope observation. Buffer A for 5 slides: 25 ml 0.05M Tris, pH 7.6, 2.5 ml 1M Imidazole, 15 ml sterile water, 2 ml DAB 5 mg/ml, 5 ml 10% ammonium nickel, 30 μ l 1% H₂O₂.

The same antibodies were used for an immunohistochemical study, according to the technique briefly described below, on paraffined slides obtained by microtome section of brain collected post mortem from MS and from controls who had died from non-neurological pathologies.

The results of the analysis are summarized below:

There is no labeling of the "non-MS" and MS brains in the "normal" (non-lesioned) white substance and gray substance with the different anti-MRP8, MRP14 and GM2A antibodies. A nonspecific reactivity did not make it possible to interpret the results with the anti-saposin B antibody in this immunohistochemical application.

On the other hand, the following are noted in the plaque zones of MS brains:

- an anti-MRP14 reactivity in the macrophage and microglial cells, having a relatively homogeneous distribution over the entire stretch of the demyelination zones (plaques),

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- a lower (less frequent) anti-MRP8 reactivity essentially linked to perivascular lymphoid infiltrates

5 - a clear anti-GM2A reactivity in the macrophages and microgliocytes of the plaque zones, with a particular density in the zones constituting the "glial wall" at the peripheral limit of a plaque. Labeling of a few astrocytes was also observed in the demyelination zones.

10

These different observations show that there is a particular hyperexpression of MRP-14 and GM2A proteins in the cultures of MS monocytes producing a gliotoxic activity in their supernatant, as well as in the zones
15 defining demyelination plaques in the MS brains. They therefore reflect the reality of the coincidence between their abnormal coexpression, the production of gliotoxic activity and the demyelination lesions.

20 Furthermore, their abnormal production in the context of MS, in macrophage blood cells as well as in those of the brain, indicates that it is justified to carry out their assay in biological fluids to correlate their quantity with the lesional and inflammatory activity of
25 MS.

Example 21: Measurement of the activity of the T cells by proliferation of the T cells (Sredni et al., 1981).

30 The T cells are washed twice in culture medium in order to remove any trace of IL2 present in the initial culture medium. B lymphocytes (EBV-LCL) or monocytes/macrophages taken as antigen-presenting cells are irradiated at 10 000 rads, and washed twice with
35 culture medium (RPMI). 2×10^4 T cells (2×10^5 cells/ml) and 2×10^4 irradiated autologous B cells (2×10^5 cells/ml) are incubated together in the presence of an increasing antigen concentration range in a final volume of 200 μ l in microwells. After 48 hours of culture at 37°C, 1 μ Ci

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of 3H-thymidine in 50 µl of RPMI medium is added to each well. The T cells, the only cells which divide, incorporate the tritiated thymidine into the DNA. After 18 hours of culture, the cells of each microwell are harvested on glass wool pastilles by aspiration. After osmotic lysis of the cells, the radioactivity incorporated into the DNA is absorbed onto the pastilles (cell Harvester 530, Inotech). Each dried pastille is placed in a plastic tube which contains 2 ml of scintillant; the radioactivity adsorbed on each of the pastilles is quantified in a liquid scintillation beta counter (LKB Rackbeta 1217). The results are expressed as an arithmetic mean of cpm/culture ("counts per minute").

15

Example 22: Protocol for detecting the association between the peptides and the histocompatibility molecules (approach APC transformed with a peptide binding to MHC I).

20

1) Materials:

The sources of histocompatibility molecules are currently of two main types: mutant cells and purified histocompatibility molecules.

25

The mutant cell used is the human T2 cell which and a variant of the T1 line produced by fusion of the CEM T lymphoma and of the 721.174 B lymphoma (Salter and Cresswell Embo J 1986, 5: 943-949). This cell, which lacks peptide transporters, contains heavy chains of class I molecules free of peptides which will be able to accept exogenous peptides.

30

Class I histocompatibility molecules purified by affinity chromatography from human B cell lines transformed with EBV can also be used. In this case, the endogenous peptides should be removed by a treatment with 1.5 M urea and 12.5 mM sodium hydroxide

35

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(pH 11.7) for 1 hour at 4°C, followed by their removal by a desalting column (PDLO, Pharmacia). The histocompatibility molecules are immediately placed in contact with the peptides to be tested in a PBS buffer
5 with 0.05% Tween 20, 2 mM EDTA, 0.1% NP40 and 6 mM CHAPS, in the presence of 2 µg/ml B2m to facilitate reassociation (Gnjatic et al., Eur J Immunol 1995 25: 1638-1642).

10 The peptides tested have in general 8 to 10 residues, sometimes 11 or 12. They were synthesized by Néosystems (Strasbourg), or by Chiron mimotopes (Victoria, Australia). They are used at concentrations varying from 100 µM to 0.1 nM.

15

2) Protocol for assembly (Connan et al., Eur J Immunol 1994, 24: 777; Couillin et al. Eur J Immunol 1995, 25: 728-732).

20 Aliquots of 8.105 cells in a volume of 64 µl, distributed in Eppendorf microfuge tubes, are brought into contact with a lysis buffer containing 10 mM PBS, pH 7.5, 1% NP40, protease inhibitors (1 mM PMSF, 100 µM iodoacetamide, 2 µg/ml aprotinin, 10 µM leupeptin,
25 10 µM pepstatin and 10 µg/ml trypsin inhibitor). The lysis is performed in the presence of the peptides to be tested for 30 minutes or 1 hour at 37°C. After removing the nonsolubilized material by centrifugation at 15 000 revolutions/minute at 4°C, the supernatant
30 and supplemented with 140 µl of PBS containing 0.05% Tween 20, 3 mM of sodium azide, 1 mM PMSF and 10 mg/ml of bovine albumin. Each sample is incubated for 20 hours at 4°C in 2 wells of a microtiter plate of the Nunc type, Maxisorb, previously coated with a
35 monoclonal antibody (10 µg/ml in PBS) which recognizes the histocompatibility molecules having conforming conformation(s) for the presentation of peptides and similar to that (those) present at the surface of the cells. The antibody-coated plate is saturated

beforehand with bovine albumin at 10 mg/ml in PBS-Tween before placing the sample. The second antibody which allows the detection of the assembly of the histocompatibility molecules is directed against B2m. It is coupled either to biotin (NHS-LC biotin, Pierce) or to alkaline phosphatase (P-552, Sigma) and is incubated at 2 µg/ml for one hour at 37°C. In the case of the use of biotin, an incubation of 45 minutes at 20-25°C with streptavidin coupled to alkaline phosphatase (E-2636, Sigma) is carried out. The activity of alkaline phosphatase is measured using, as substrate, 4-methylumbelliferyl phosphate (M-8883, Sigma) at 100 µM in 50 mM diethanolamine, pH 9.5 with 1 mM MgCl₂. The reading is carried out at 340/460 nm with the aid of a cytofluorimeter.

3) Stability of the HLA/peptide complexes:

The stability of the abovementioned complexes was studied because it determines the good presentation of the antigen and the induction of the T response. To this effect, either purified HLA or the T2 cell lysate was used. With purified HLA, the endogenous peptides were removed (as described in 2)) and then it was brought into contact with the peptide to be tested in an Eppendorf tube at 37°C, for periods varying from a few minutes to several days. The following incubation phase on a 96-well plate (as described in 2) with the anti-HLA antibody is performed for one hour at 37°C. The revealing is carried out in a conventional manner. With the T2 cell lysate, all the incubations are also carried out at 37°C, after addition of all the protease inhibitors.

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JC13 Rec'd PCT/PTO 15 JAN 2002

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CLAIMS

1. The use of at least one polypeptide comprising at least one fragment of a protein to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, preventing or treating a pathological condition associated with multiple sclerosis, said protein being chosen from proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28 and SEQ ID No. 29 and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to SEQ ID No. 8 and SEQ ID No. 10 to SEQ ID No. 29, and the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B.
2. The use as claimed in claim 1, of at least two polypeptides in combination as defined in claim 1.
3. Use according to claim 1, characterized in that said protein is chosen from the proteins whose peptide sequence in the native state corresponds to SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 8, SEQ ID No. 17 and SEQ ID No. 24 and the peptide sequences which exhibit at least 70% identity,

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preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 8, SEQ ID No. 17 and SEQ ID No. 24.

5

4. The use as claimed in claim 3, of five polypeptides in combination, as defined in claim 3.

10

5. The use as claimed in any one of claims 1 to 4, characterized in that the peptide sequence of said polypeptide comprises a sequence chosen from any one of SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 8, SEQ ID No. 17 and SEQ ID No. 24.

15

6. The use as claimed in any one of claims 1 to 4, characterized in that the peptide sequence of said polypeptide consists of a sequence chosen from any one of SEQ ID No. 2, SEQ ID No. 4, SEQ ID No. 8, SEQ ID No. 17 and SEQ ID No. 24.

20

7. The use of a polypeptide fragment defined in claim 1 or in claim 3 for the preparation of an immunogenic peptide, characterized in that said peptide comprises all or part of at least one of the sequences designated by the references SEQ ID No. 58 to 65.

25

8. The use of at least one nucleotide fragment to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological condition associated with multiple sclerosis, according to which said nucleotide fragment is chosen from fragments which encode at least one fragment of a protein as defined in claim 1.

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9. The use as claimed in claim 8, characterized in that said nucleotide fragment encodes said protein.
- 5 10. The use of at least one nucleotide fragment to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological condition associated with multiple sclerosis, according to which said fragment is a
10 fragment of a nucleic sequence chosen from any one of SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 35, SEQ ID No. 36, SEQ ID No. 37, SEQ ID No. 38, SEQ ID
15 No. 39, SEQ ID No. 40, SEQ ID No. 41, SEQ ID No. 42, SEQ ID No. 43, SEQ ID No. 44, SEQ ID No. 45, SEQ ID No. 46 and SEQ ID No. 47, SEQ ID No. 48, SEQ ID No. 49 and SEQ ID No. 50, SEQ ID No. 51, SEQ ID No. 52, SEQ ID No. 53, SEQ ID
20 No. 54, SEQ ID No. 55, SEQ ID No. 56, SEQ ID No. 57, SEQ ID No. 67, SEQ ID No. 66, SEQ ID No. 69, SEQ ID No. 70 and SEQ ID No. 71, and their complementary sequences.
- 25 11. The use of a ligand specific for a polypeptide or for a nucleotide fragment as claimed in any one of the preceding claims to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating,
30 preventing or treating a pathological condition associated with multiple sclerosis.
12. A method for detecting at least one protein associated with multiple sclerosis, in a
35 biological sample, characterized in that the biological sample is brought into contact with at least one ligand specific for at least one polypeptide as defined in claim 1, and then the

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formation of a complex between said polypeptide and said ligand is detected.

- 5 13. The method as claimed in claim 12, characterized in that said ligand is a monoclonal antibody, a polyclonal antibody, a receptor, a substrate for enzymatic activity or an enzyme for which said polypeptide is a cofactor.
- 10 14. A method for detecting at least one ligand associated with multiple sclerosis, in a biological sample, characterized in that the biological sample is brought into contact with at least one polypeptide as defined in claim 1, and
15 then the formation of a complex between said polypeptide and said ligand is detected.
- 20 15. The method as claimed in claim 14, characterized in that the ligand is an antibody, a receptor, a substrate for enzymatic activity or an enzyme for which said polypeptide is a cofactor.
- 25 16. The method as claimed in any one of claims 12 to 15, characterized in that the sequence of said polypeptide comprises a peptide sequence chosen from any one of SEQ ID No. 1 to 8 and SEQ ID No. 10 to 29.
- 30 17. The method as claimed in any one of claims 12 to 15, characterized in that the sequence of said polypeptide consists of a peptide sequence chosen from any one of SEQ ID No. 1 to 8 and SEQ ID No. 10 to 29.
- 35 18. The method as claimed in any one of claims 12 to 15, characterized in that the biological sample is urine, cerebrospinal fluid or serum.

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19. A polypeptide, characterized in that it comprises at least one fragment of a protein whose peptide sequence corresponds to SEQ ID No. 9, said fragment comprising at least one mutation in relation to the reference sequence SEQ ID No. 8.
5
20. The polypeptide as claimed in claim 19, characterized in that it comprises at least two mutations in relation to the reference sequence SEQ ID No. 8.
10
21. The polypeptide as claimed in claim 20, characterized in that it is chosen from the polypeptides which comprise the sequence SEQ ID No. 68 and the sequence SEQ ID No. 72.
15
22. The polypeptide as claimed in one of claims 19 to 21, characterized in that it comprises a protein whose peptide sequence corresponds to SEQ ID No. 9.
20
23. The polypeptide as claimed in one of claims 19 to 21, characterized in that it consists of a protein whose peptide sequence corresponds to SEQ ID No. 9.
25
24. The use of at least one polypeptide as claimed in any one of claims 19 to 23 to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological condition associated with multiple sclerosis.
30
25. The use as claimed in claim 24, characterized in that said polypeptide is used in the form of a mixture with at least one polypeptide as defined in any one of claims 1 to 6.
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26. A method for detecting at least one ligand associated with multiple sclerosis, in a biological sample, characterized in that the biological sample is brought into contact with at least one polypeptide as defined in any one of claims 19 to 23, and then the formation of a complex between said polypeptide and the ligand is detected.
27. The method as claimed in claim 26, characterized in that the biological sample is in addition brought into contact with at least one polypeptide as defined in any one of claims 1 to 5.
28. The method as claimed in claim 26 or 27, characterized in that said ligand is an antibody, a receptor, a substrate for enzymatic activity or an enzyme for which said polypeptide is a cofactor.
29. A method for detecting at least one polypeptide as defined in any one of claims 19 to 23, in a biological sample, characterized in that the biological sample is brought into contact with at least one ligand specific for said polypeptide, and then the formation of a complex between said polypeptide and said ligand is detected.
30. The method as claimed in claim 29, characterized in that said ligand is a monoclonal antibody, a polyclonal antibody, a receptor, a substrate for enzymatic activity or an enzyme for which said polypeptide is a cofactor.
31. The method as claimed in claim 27 or 28, characterized in that the biological sample is brought into contact with a ligand as defined in either of claims 28 and 30 and at least one ligand specific for at least one polypeptide as defined

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in any one of claims 1 to 5, and then the formation of complexes between said polypeptides and said ligands specific for said polypeptides is detected.

5

32. The method as claimed in claim 31, characterized in that the ligand is a monoclonal antibody, a polyclonal antibody, a receptor, a substrate for enzymatic activity or an enzyme for which said polypeptide is a cofactor.

10

33. A nucleotide fragment, characterized in that it encodes a polypeptide as defined in any one of claims 19 to 23.

15

34. The use of a nucleotide fragment to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, prognosticating, preventing or treating a pathological condition associated with multiple sclerosis, according to which said nucleotide fragment is the nucleotide fragment defined in claim 33, optionally in combination with at least one nucleotide fragment as defined in any one of claims 8 to 10, and the fragments complementary to said fragments.

20

25

35. The method as claimed in any one of claims 26 to 32, characterized in that the biological sample is urine, cerebrospinal fluid or serum.

30

36. The method as claimed in any one of claims 26 to 32, characterized in that the degenerative and/or autoimmune disease is multiple sclerosis.

35

37. A method for detecting, in a sample of biological fluid, at least one polypeptide as defined in any one of claims 1 to 5 or in any one of claims 19 to 23, according to which, optionally after

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purification of said sample, the mass profile obtained from said sample is analyzed by mass spectrometry and compared with a reference mass profile.

5

38. The use of at least one polypeptide as defined in claim 1 to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, preventing, or treating a pathological condition associated with multiple sclerosis, and preferably of at least one polypeptide as defined in claim 5.

10

39. The use as claimed in claim 38, in which the peptide sequences comprise the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from the precursor of the ganglioside GM2 activator and saposin B.

15

20

40. The use as claimed in either of claims 38 or 39, which is associated with the use of a detection of a gliotoxic activity.

25

41. A method for detecting, in a sample, a value for the concentration of at least one polypeptide as claimed in any one of claims 38 to 40, said concentration being associated with a pathological condition, characterized in that said polypeptide is assayed, the assay making it possible to obtain a concentration value which is compared with a threshold value representative of multiple sclerosis.

30

42. The method as claimed in claim 41, in which the threshold value is obtained by an ELISA test for a urine sample, this value being:

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- 400 ng/ml for the precursor of the ganglioside GM2 activator, for the GM2AP84 antibody, and
- 2 µg/ml for saposin B, for the SAPB84 antibody.

5

43. The method as claimed in claim 12, characterized in that the biological sample consists of cells or supernatants of said cells from a patient likely to suffer from multiple sclerosis.

10

44. The method as claimed in claim 43, in which the biological sample consists of monocyte or macrophage cells or of supernatants of these cells.

15

45. The method as claimed in either of claims 43 and 44, in which the biological sample consists of cells in culture or of supernatants of these cells in culture, after a period of between 6 and 12 days of culture, preferably after 9 days.

20

46. The method as claimed in either of claims 43 and 44, in which the biological sample consists of cells, ex vivo, preferably monocytes or macrophages.

25

47. The use of at least one polypeptide as defined in claim 1 for testing the efficacy of a therapeutic agent.

30

48. The use of at least one polypeptide comprising at least one fragment of a protein for the preparation of a pharmaceutical composition for treating multiple sclerosis, said protein being chosen from proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8, SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID

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No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID
 No. 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID
 No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID
 No. 21, SEQ ID No. 22, SEQ ID No. 23, SEQ ID
 5 No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No.
 27, SEQ ID No. 28 and SEQ ID No. 29 and the
 peptide sequences which exhibit at least 70%
 identity, preferably at least 80% identity and
 advantageously at least 98% identity with any one
 10 of the peptide sequences SEQ ID No. 1 to 29, and
 the peptide sequences or the fragments of said
 sequences belonging to the same family of proteins
 chosen from Perlecan, the precursor of the
 retinol-binding plasma protein, precursor of the
 15 ganglioside GM2 activator, calgranulin and
 saposin.

49. The use as claimed in claim 47 or 48,
 characterized in that the polypeptide is chosen
 20 from SEQ ID No. 2, 4, 8, 9, 17, 24.

50. The use of at least one nucleotide fragment, to
 test the efficacy of a therapeutic agent for a
 pathological condition associated with multiple
 25 sclerosis, according to which said nucleotide
 fragment is chosen from the fragments which encode
 at least one fragment of a protein, said protein
 being chosen from proteins whose peptide sequence
 in the native state corresponds to SEQ ID No. 1,
 30 SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID
 No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8,
 SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID
 No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No.
 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18,
 35 SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ
 ID No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID
 No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No.
 28 and SEQ ID No. 29 and the peptide sequences
 which exhibit at least 70% identity, preferably at

least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, the fragments complementary to said fragments and the fragments which encode the peptide sequences or the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B.

51. The use, to test the efficacy of a therapeutic agent for a pathological condition associated with multiple sclerosis, of recombinant proteins and/or proteins encoded by all or part of the nucleotide fragments defined in claim 50.

52. The use of at least one nucleotide fragment for the preparation of a pharmaceutical composition for treating multiple sclerosis, according to which said nucleotide fragment is chosen from the fragments which encode at least one fragment of a protein, said protein being chosen from proteins whose peptide sequence in the native state corresponds to SEQ ID No. 1, SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID No. 7, SEQ ID No. 8, SEQ ID No. 9, SEQ ID No. 10, SEQ ID No. 11, SEQ ID No. 12, SEQ ID No. 13, SEQ ID No. 14, SEQ ID No. 15, SEQ ID No. 16, SEQ ID No. 17, SEQ ID No. 18, SEQ ID No. 19, SEQ ID No. 20, SEQ ID No. 21, SEQ ID No. 22, SEQ ID No. 23, SEQ ID No. 24, SEQ ID No. 25, SEQ ID No. 26, SEQ ID No. 27, SEQ ID No. 28 and SEQ ID No. 29 and the peptide sequences which exhibit at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No. 1 to 29, the fragments complementary to said fragments and the fragments which encode the peptide sequences or

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the fragments of said sequences belonging to the same family of proteins chosen from Perlecan, the precursor of the retinol-binding plasma protein, precursor of the ganglioside GM2 activator, calgranulin B and saposin B.

5

53. The use, for the preparation of a pharmaceutical composition for treating multiple sclerosis, of recombinant proteins and/or proteins encoded by all or part of the nucleotide fragments defined in claim 52.

10

54. The use as claimed in claim 50 or 52, characterized in that said nucleotide fragment encodes said protein.

15

55. The use as claimed in claim 54, characterized in that the polypeptides are chosen from SEQ ID No. 2, 4, 8, 9, 17, 24.

20

56. The use as claimed in claim 50, characterized in that said fragment is a fragment of a nucleic sequence chosen from any one of SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID No. 34, SEQ ID No. 35, SEQ ID No. 36, SEQ ID No. 37, SEQ ID No. 38, SEQ ID No. 39, SEQ ID No. 40, SEQ ID No. 41, SEQ ID No. 42, SEQ ID No. 43, SEQ ID No. 44, SEQ ID No. 45, SEQ ID No. 46 and SEQ ID No. 47, SEQ ID No. 48, SEQ ID No. 49 and SEQ ID No. 50, SEQ ID No. 51, SEQ ID No. 52, SEQ ID No. 53, SEQ ID No. 54, SEQ ID No. 55, SEQ ID No. 56, SEQ ID No. 57, SEQ ID No. 66, SEQ ID No. 67, SEQ ID No. 69, SEQ ID No. 70 and SEQ ID No. 71, and their complementary sequences.

25

30

35

57. The use as claimed in claim 52, characterized in that said fragment is a fragment of a nucleic sequence chosen from any one of SEQ ID No. 30, SEQ ID No. 31, SEQ ID No. 32, SEQ ID No. 33, SEQ ID

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5 No. 34, SEQ ID No. 35, SEQ ID No. 36, SEQ ID No.
37, SEQ ID No. 38, SEQ ID No. 39, SEQ ID No. 40,
SEQ ID No. 41, SEQ ID No. 42, SEQ ID No. 43, SEQ
ID No. 44, SEQ ID No. 45, SEQ ID No. 46 and SEQ ID
No. 47, SEQ ID No. 48, SEQ ID No. 49 and SEQ ID
No. 50, SEQ ID No. 51, SEQ ID No. 52, SEQ ID No.
53, SEQ ID No. 54, SEQ ID No. 55, SEQ ID No. 56,
SEQ ID No. 57, SEQ ID No. 66, SEQ ID No. 67, SEQ
ID No. 69, SEQ ID No. 70 and SEQ ID No. 71, and
10 their complementary sequences.

58. The use as claimed in claim 56 or 57,
characterized in that the nucleic sequence is
chosen from SEQ ID No. 30, 31, 42, 53.

15 59. The use of lycorine for the preparation of a
composition for preventing and/or treating
multiple sclerosis.

ABSTRACT OF DISCLOSURE

The invention concerns the use of at least one polypeptide comprising a protein fragment to obtain a diagnostic, prognostic, prophylactic or therapeutic composition for detecting, preventing or treating a pathological condition associated with a degenerative and/or neurological and/or autoimmune disease, said protein being selected among the proteins whereof the peptide sequence in native state corresponds to SEQ ID No 1, SEQ ID No 2, SEQ ID No 3, SEQ ID No 4, SEQ ID No 5, SEQ ID No 6, SEQ ID No 7, SEQ ID No 8, SEQ ID No 9, SEQ ID No 10, SEQ ID No 11, SEQ ID No 12, SEQ ID No 13, SEQ ID No 14, SEQ ID No 15, SEQ ID No 16, SEQ ID No 17, SEQ ID No 18, SEQ ID No 19, SEQ ID No 20, SEQ ID No 21, SEQ ID No 22, SEQ ID No 23, SEQ ID No 24, SEQ ID No 25, SEQ ID No 26, SEQ ID No 27, SEQ ID No 28, and SEQ ID No 29, and the peptide sequences having at least 70% identity, preferably at least 80% identity and advantageously at least 98% identity with any one of the peptide sequences SEQ ID No 1 to SEQ ID No 8 and SEQ ID No 10 to SEQ ID No 29, and the peptide sequences or fragments of said sequences belonging to a common family of proteins selected among perlecan, the precursor of the retinol-binding plasmatic protein, of the precursor of the activator of GM2 ganglioside, of calgranulin B and of saponin B.

Rabbits anti GM2

➤ **Ganglioside GM2 activator**

2 peptides of 13, 15 amino acids **rabbits 189 190**

1 peptide of 18 amino acids

MQSLMQAPLL IALGLLATP AQAHLKKPSQ

LSSFSDNCD EGKDPVIRS LTLEDPPIW

PGNVTLSVVG STSVPLSSPL KVDLYLEKEV

AGLWIKIPCT DYIGSCTFEH FCDVLDMLIP

TGEPCEPLR TYGLPCHCPF KEGTYSLPKS

EFWPDLEP SWLTTGNYRI ESVLSSGKR

LGCIKA4SLKGI

Q21

[illegible]

FIG. 1

Rabbits anti MRP14

2 peptides of 13, 19 amino acids rabbit 193
1 peptide of 17 amino acids rabbit 195-196

MTCKMSQLER NIETINTFH QYSVKLGHPD
TLNQGEFKEL VRKDLQNFLK KENKNEKVE
HIMEDDLDTN ADKQLSFEF IMLMARLTWA
SHEKMHEGDE GPGHHKPGI GEGTP

MRP1

ATG ACT TGC AAA ATG TCG CAG CTG GAA CCG AAC AAC GAG ACC ATC ATC ACC TTC CAC CAA TAC TCT CTG MAG CTG CCG CAC CCA
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L N Q G E P K E L V R R K D L Q N P L K K E N K N E K V I E
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H E D L D T N A D K Q L S F E F I M L M A R L T W A
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FIG. 2

MRP 8 assay

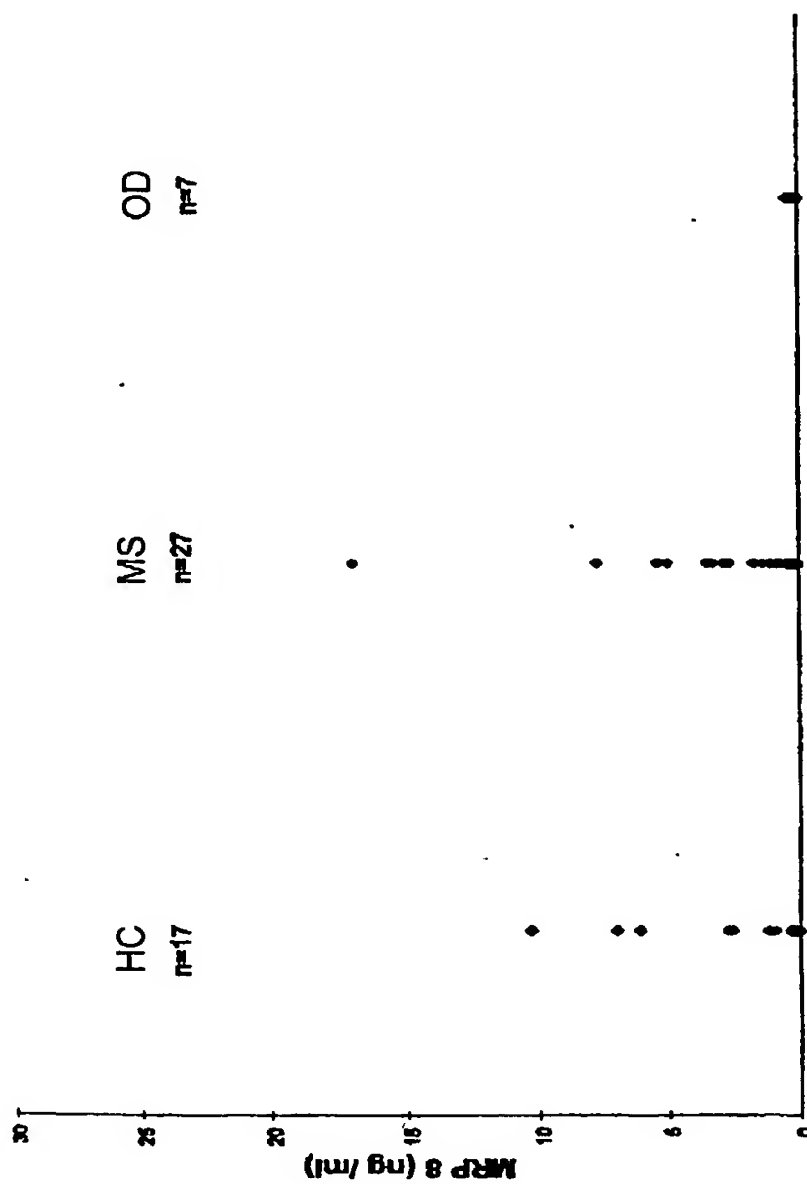


FIG. 4

MRP14 assay

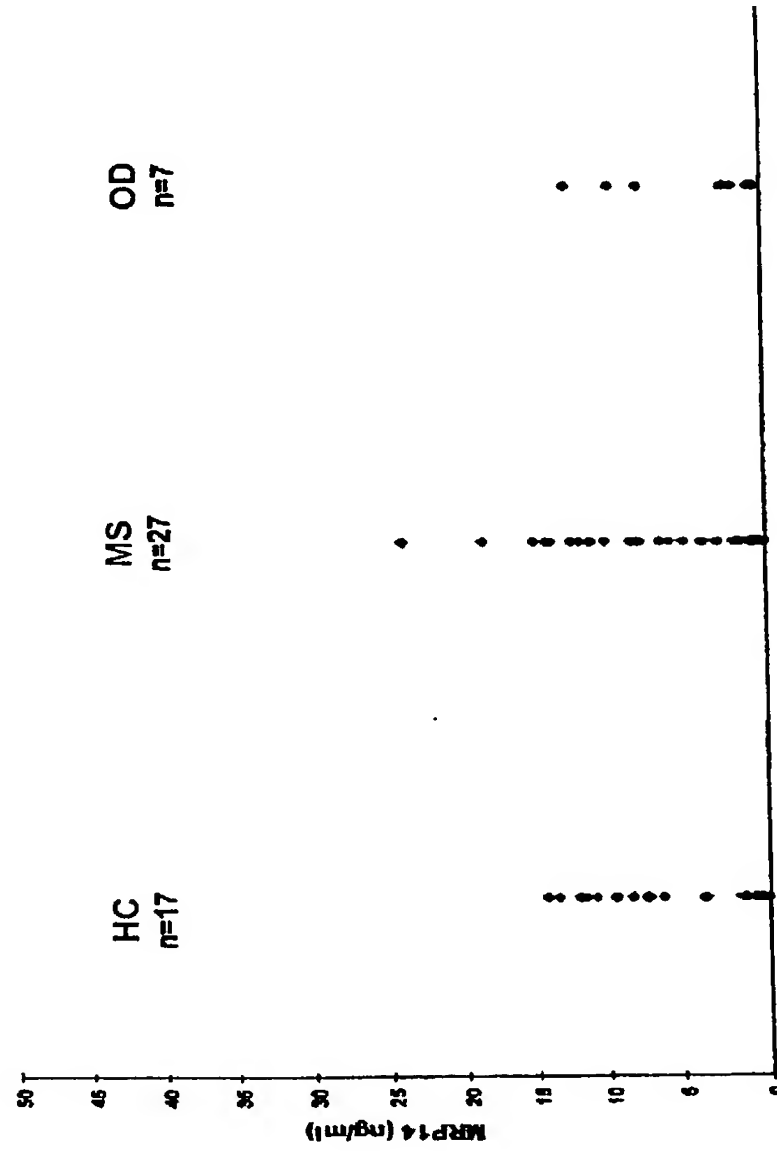
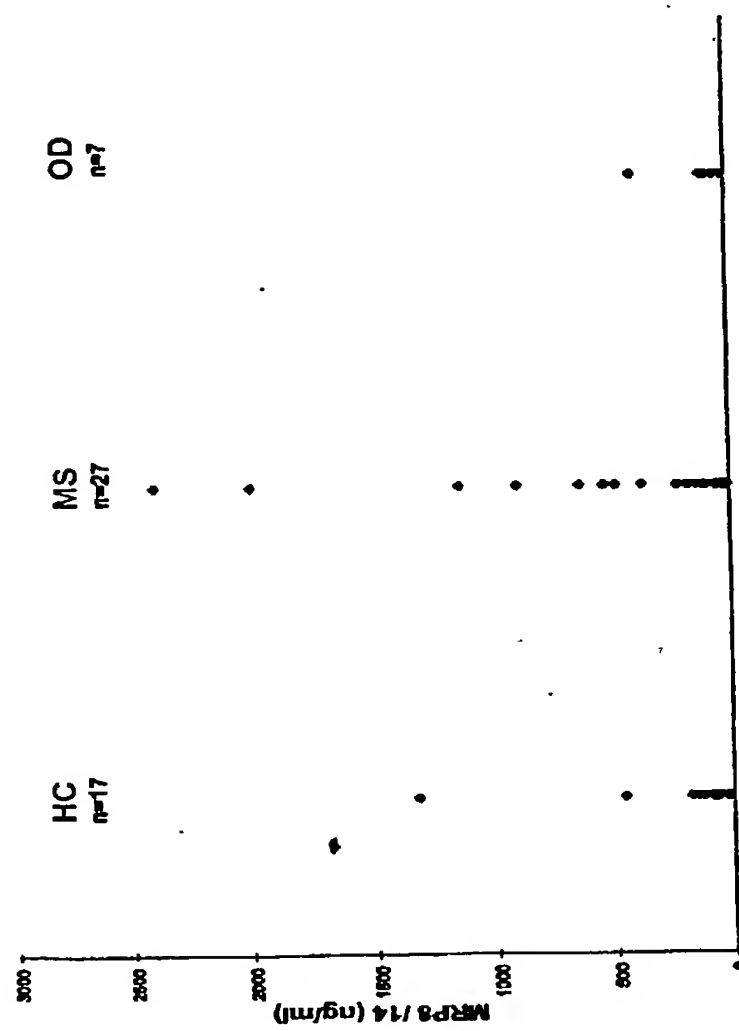


FIG. 5

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MRP8/14 assay

**FIG. 6**

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Mean urinary level per category of population (ULC)

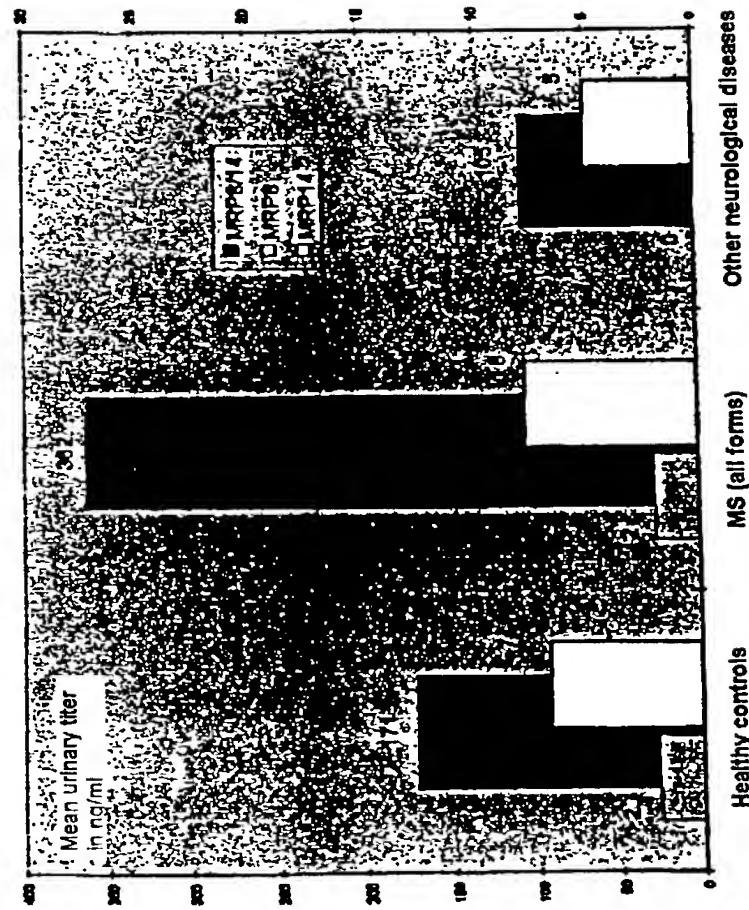
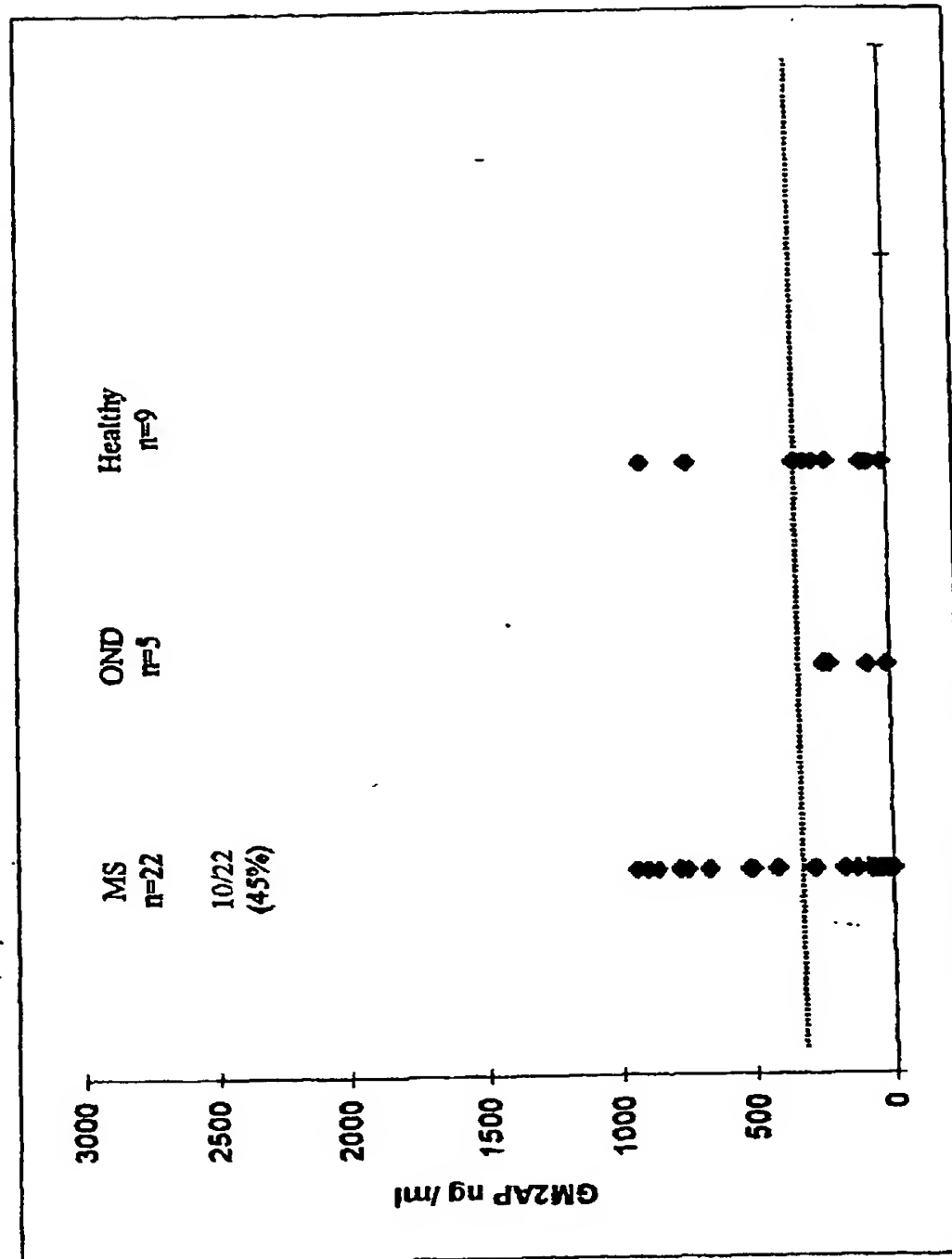


FIG. 7

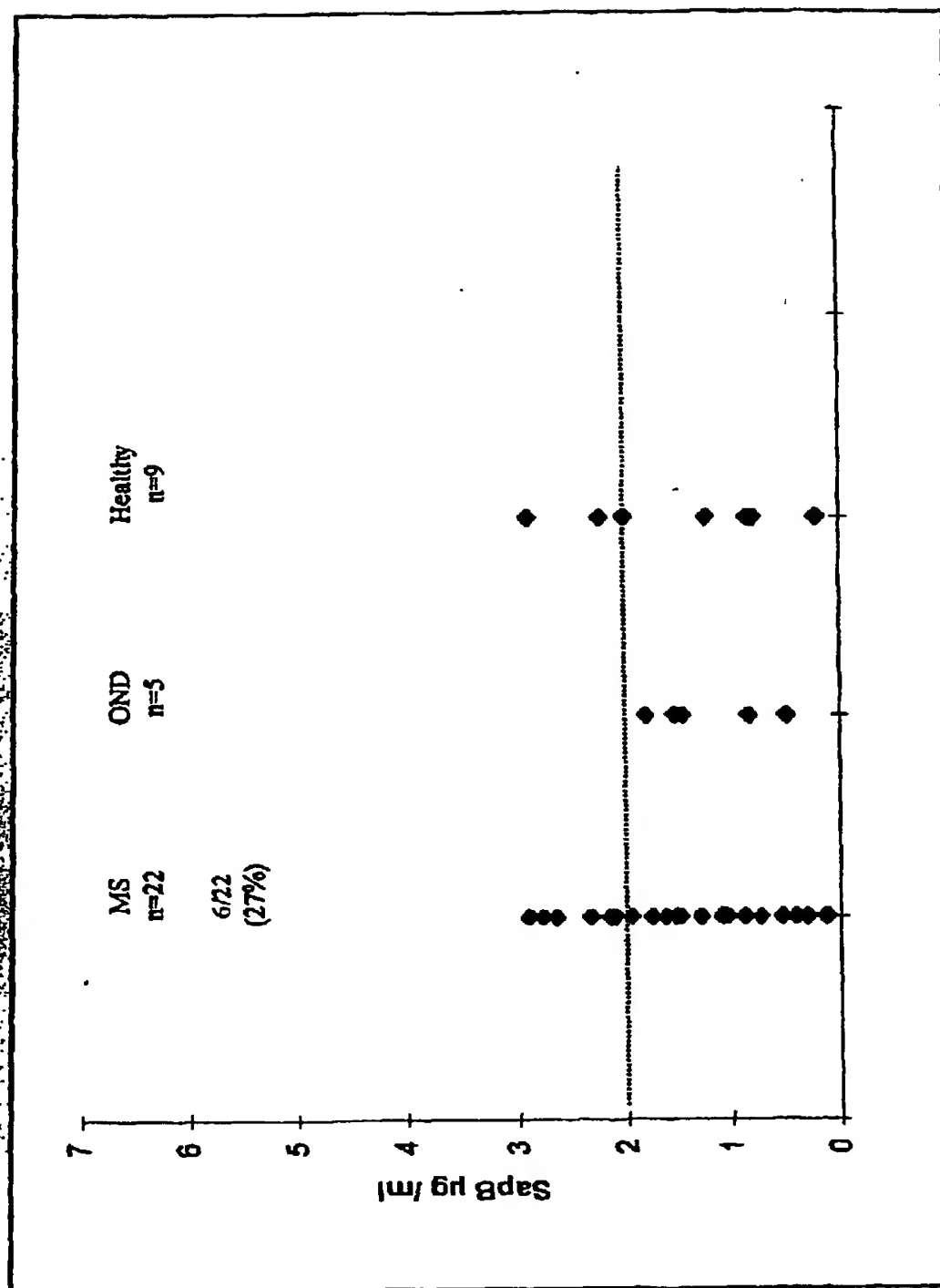
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Figure 8



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Figure 9



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Figure 10

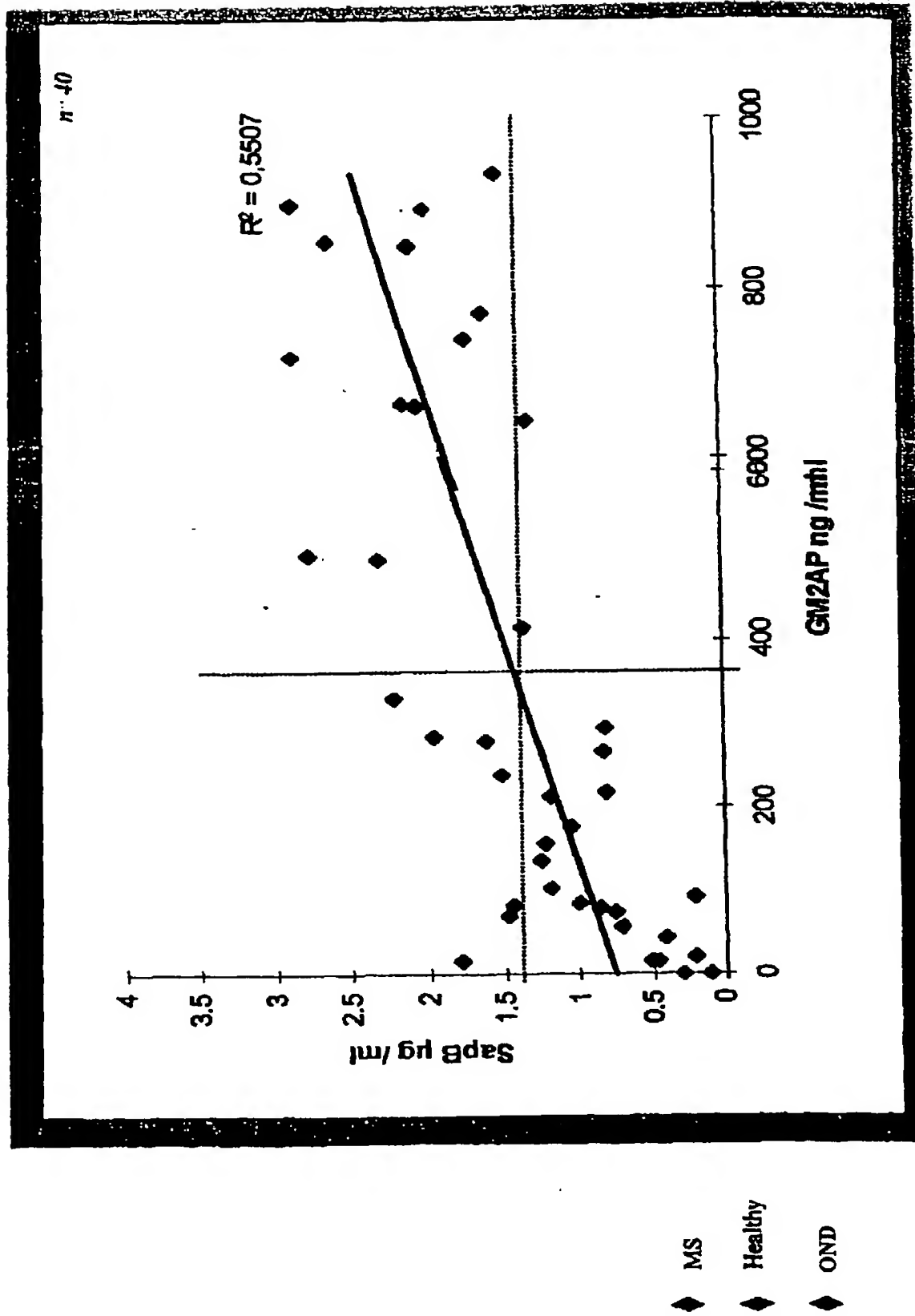
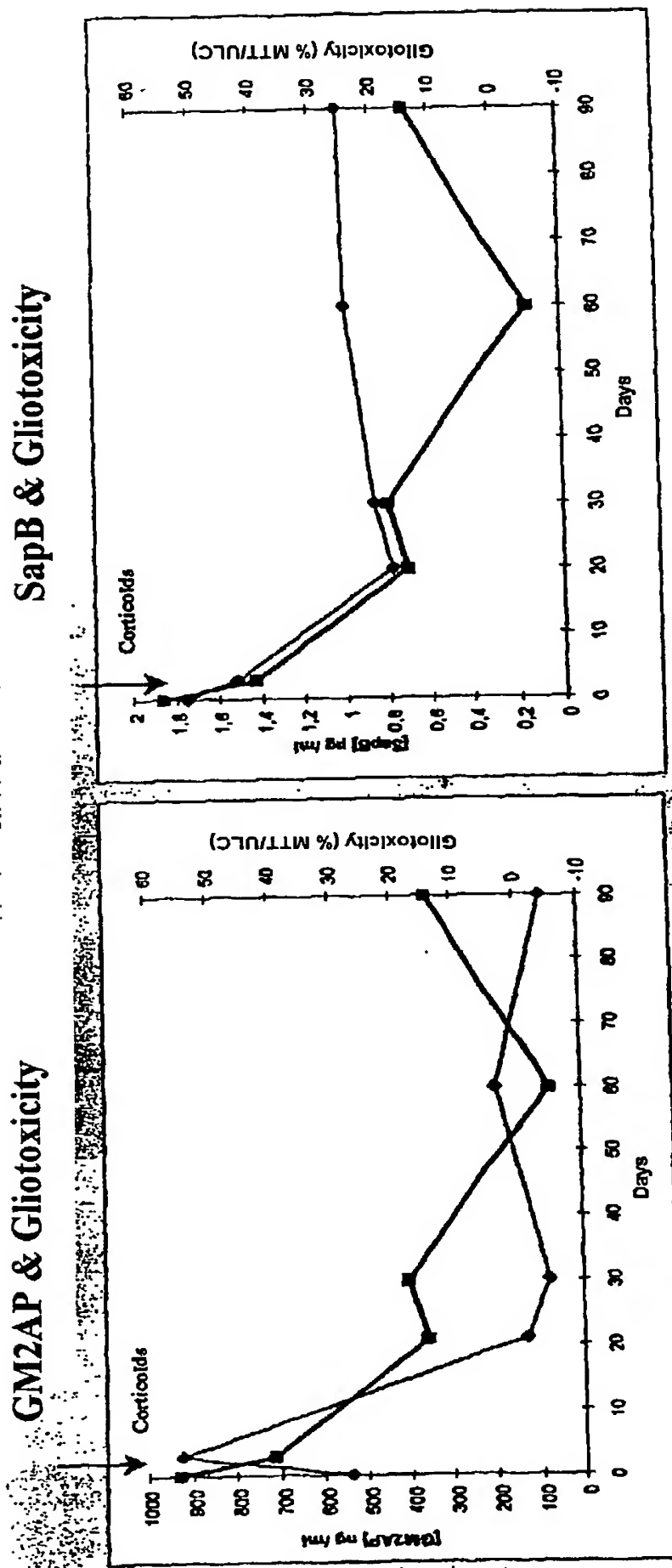
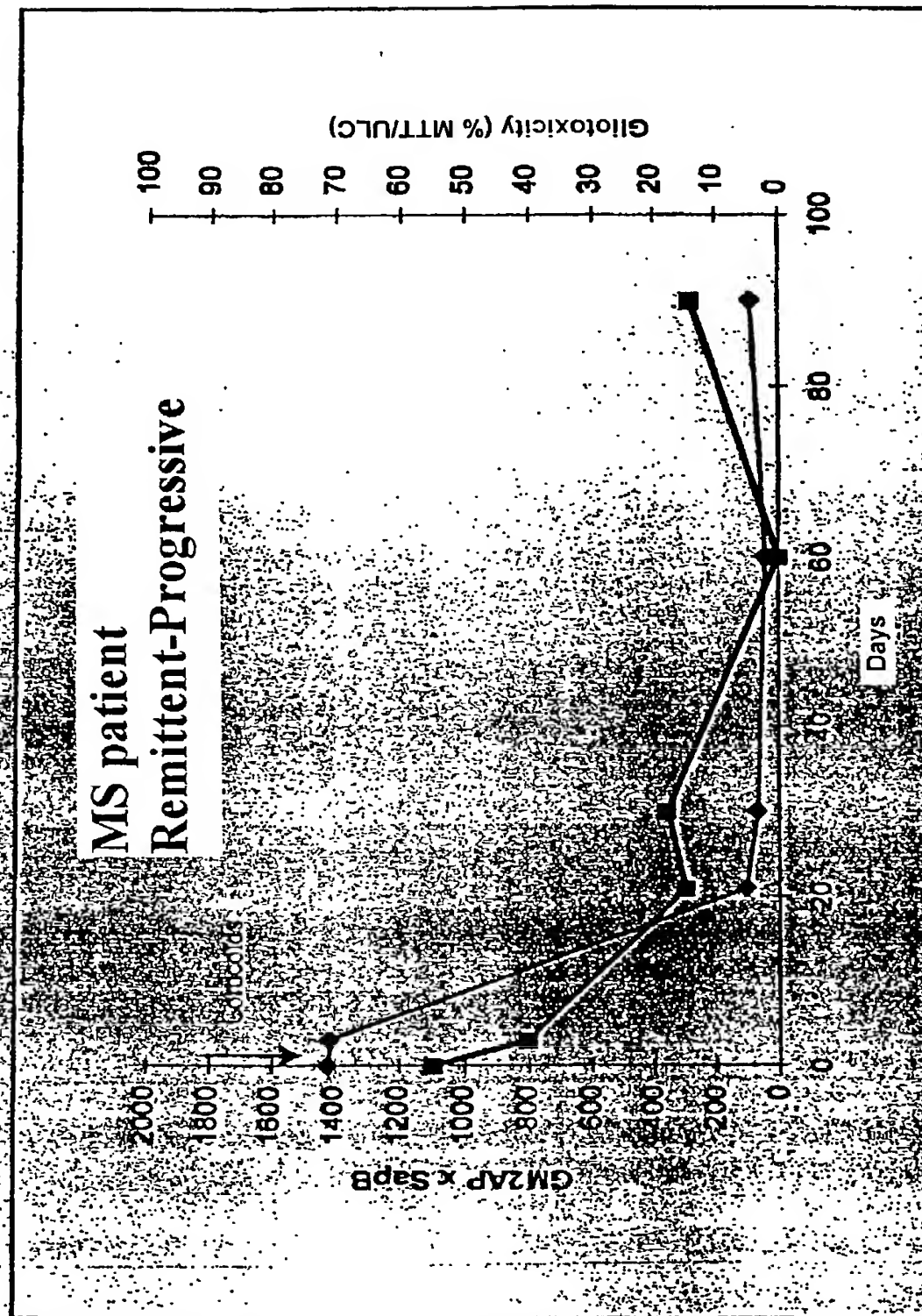


Figure 11
MS patient progressive remittent form



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Figure 12

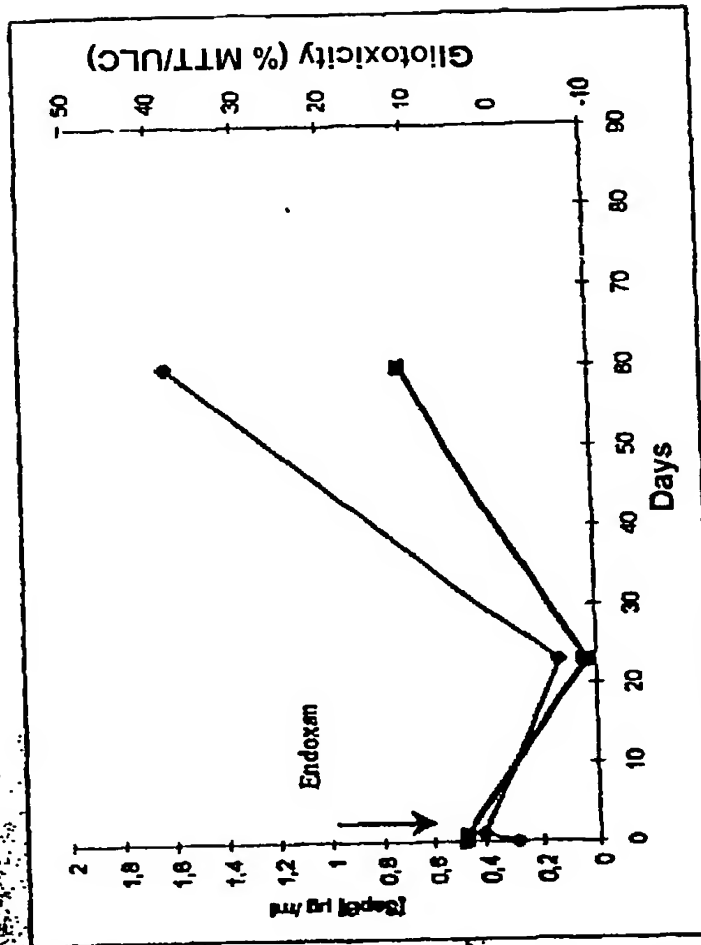


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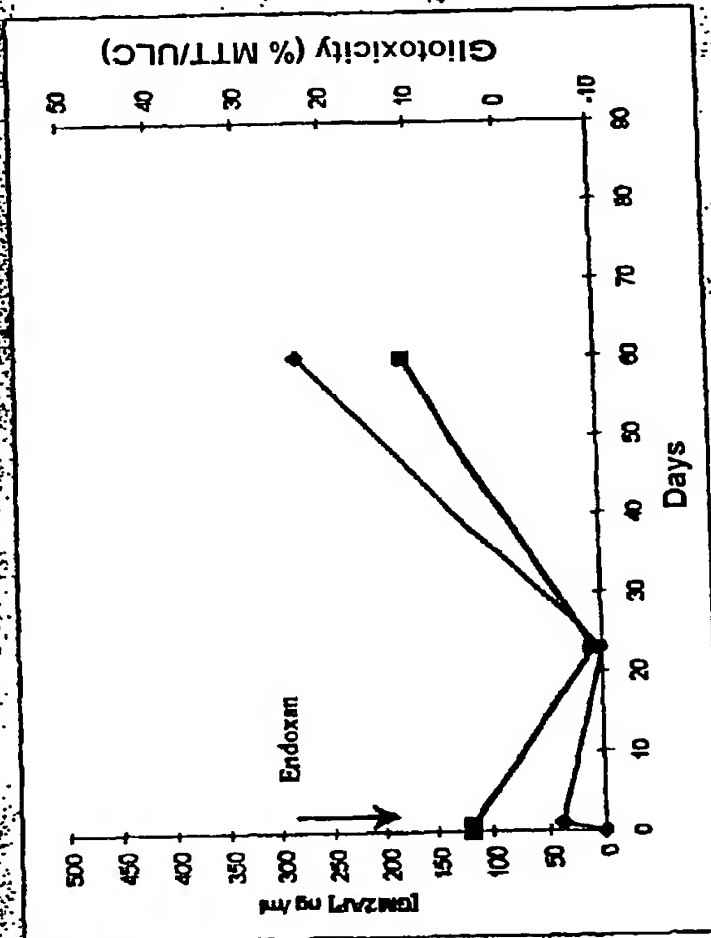
Figure 13

MS patient - Progressive

SapB & Gliotoxicity



GM2AP & Gliotoxicity



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Figure 14

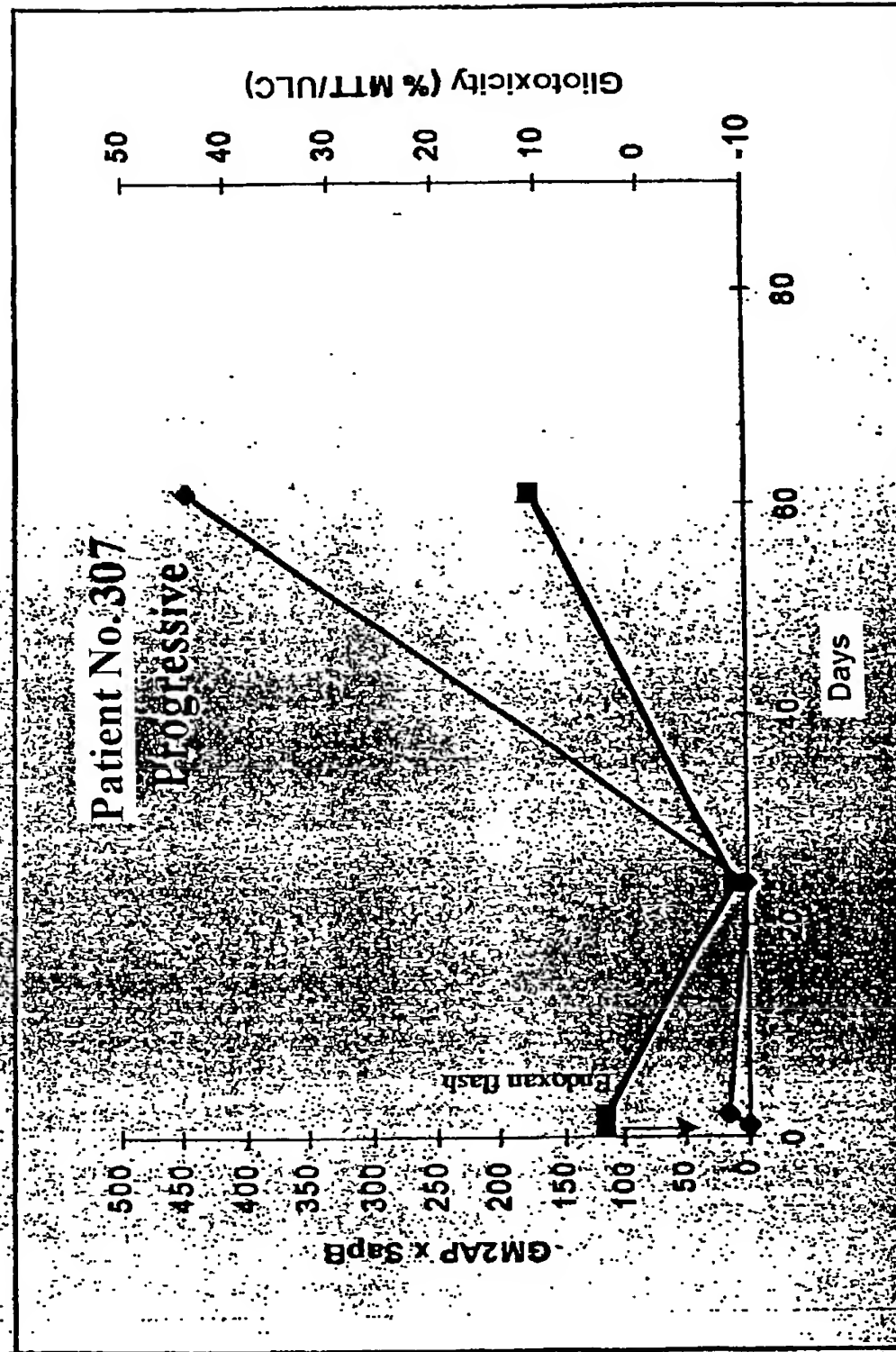
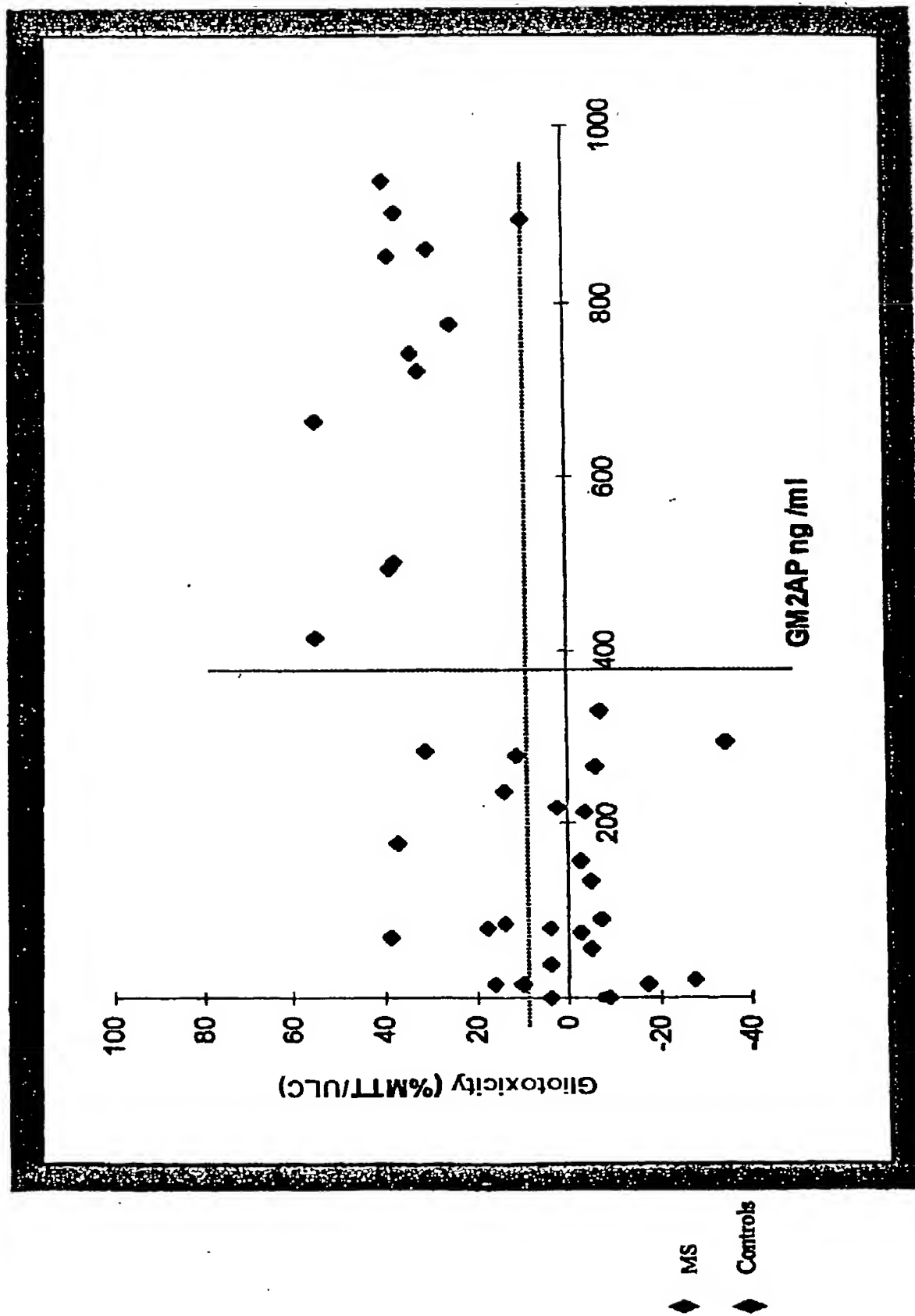


Figure 15



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Figure 16

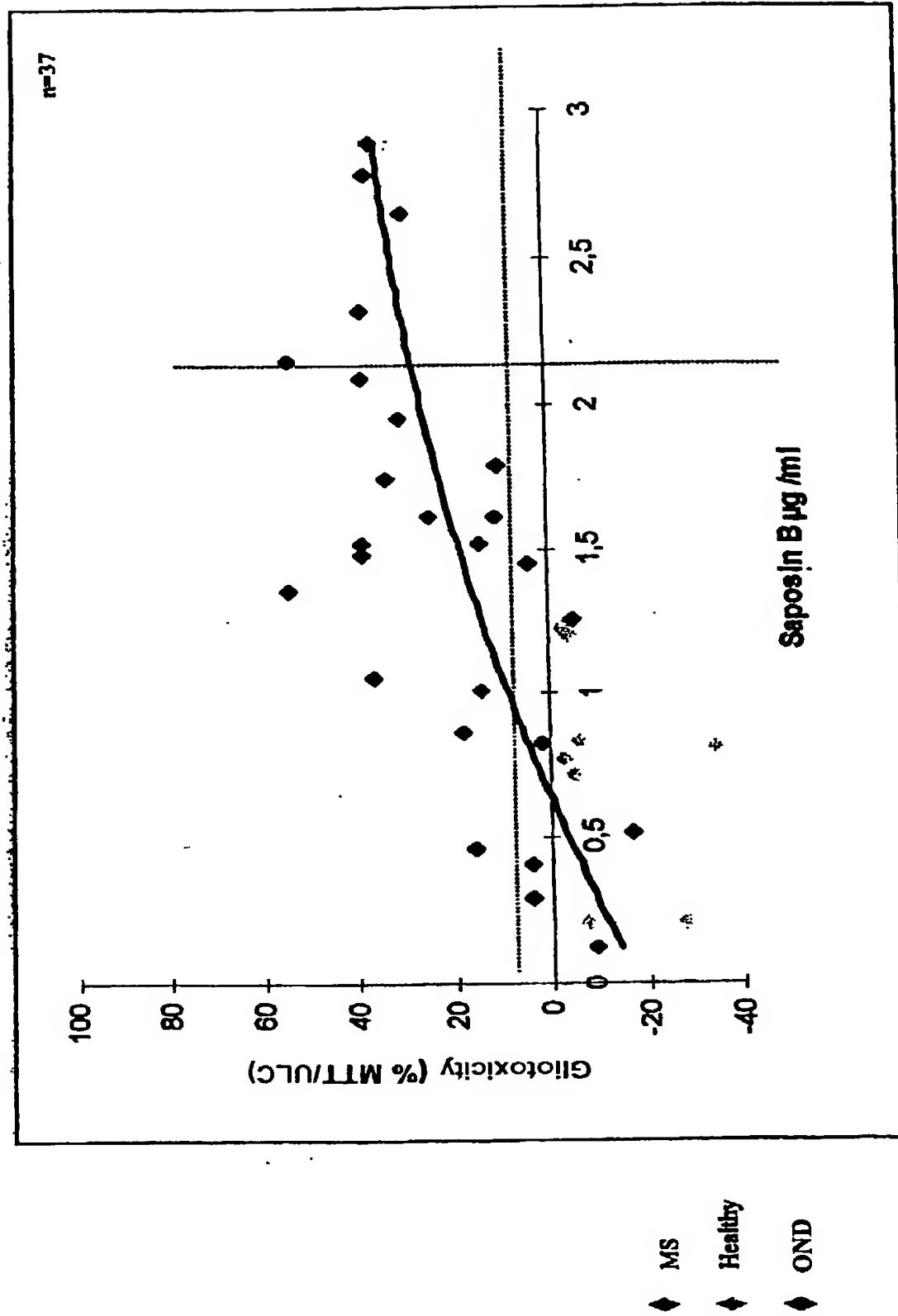


Figure 17

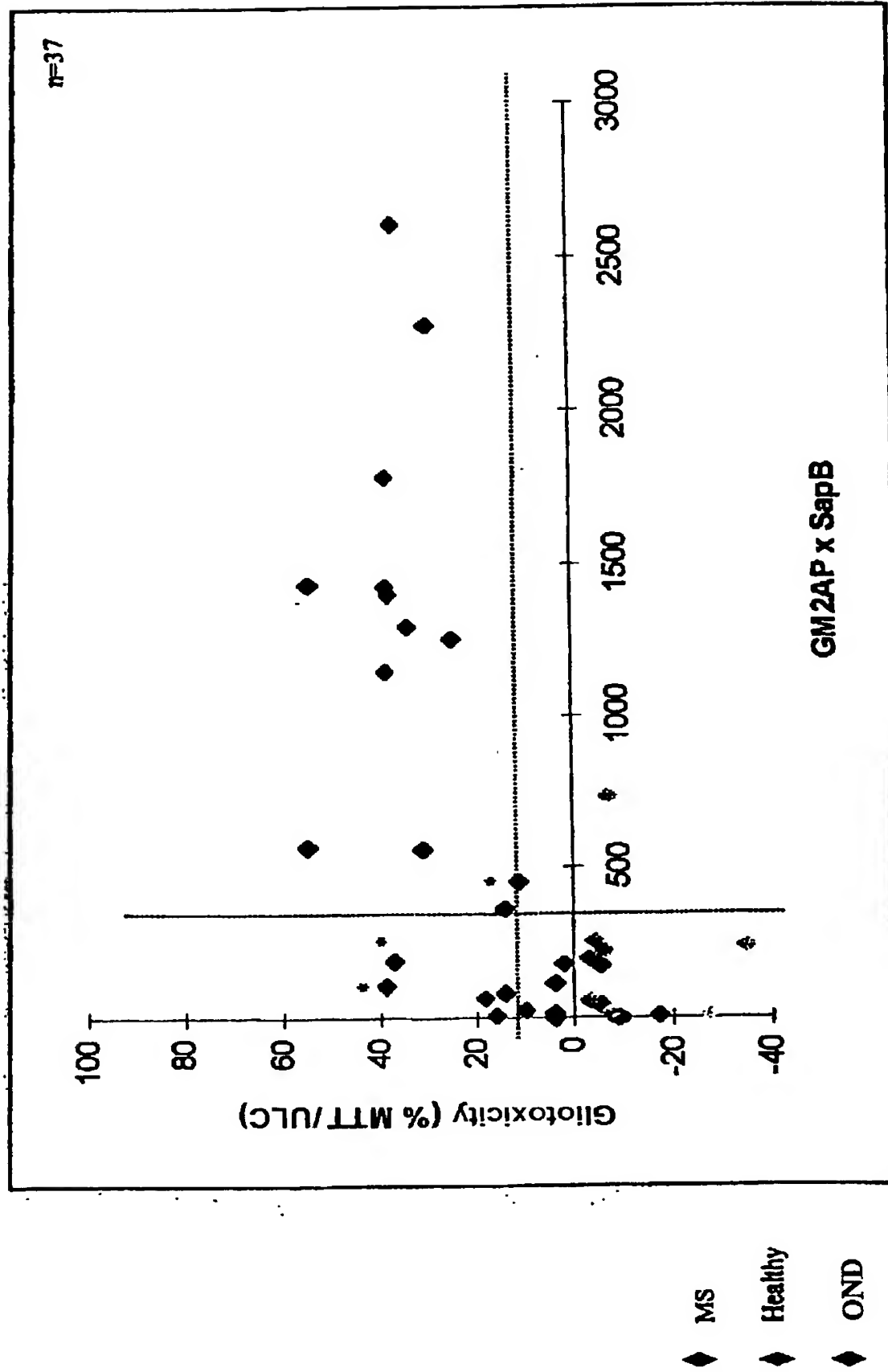
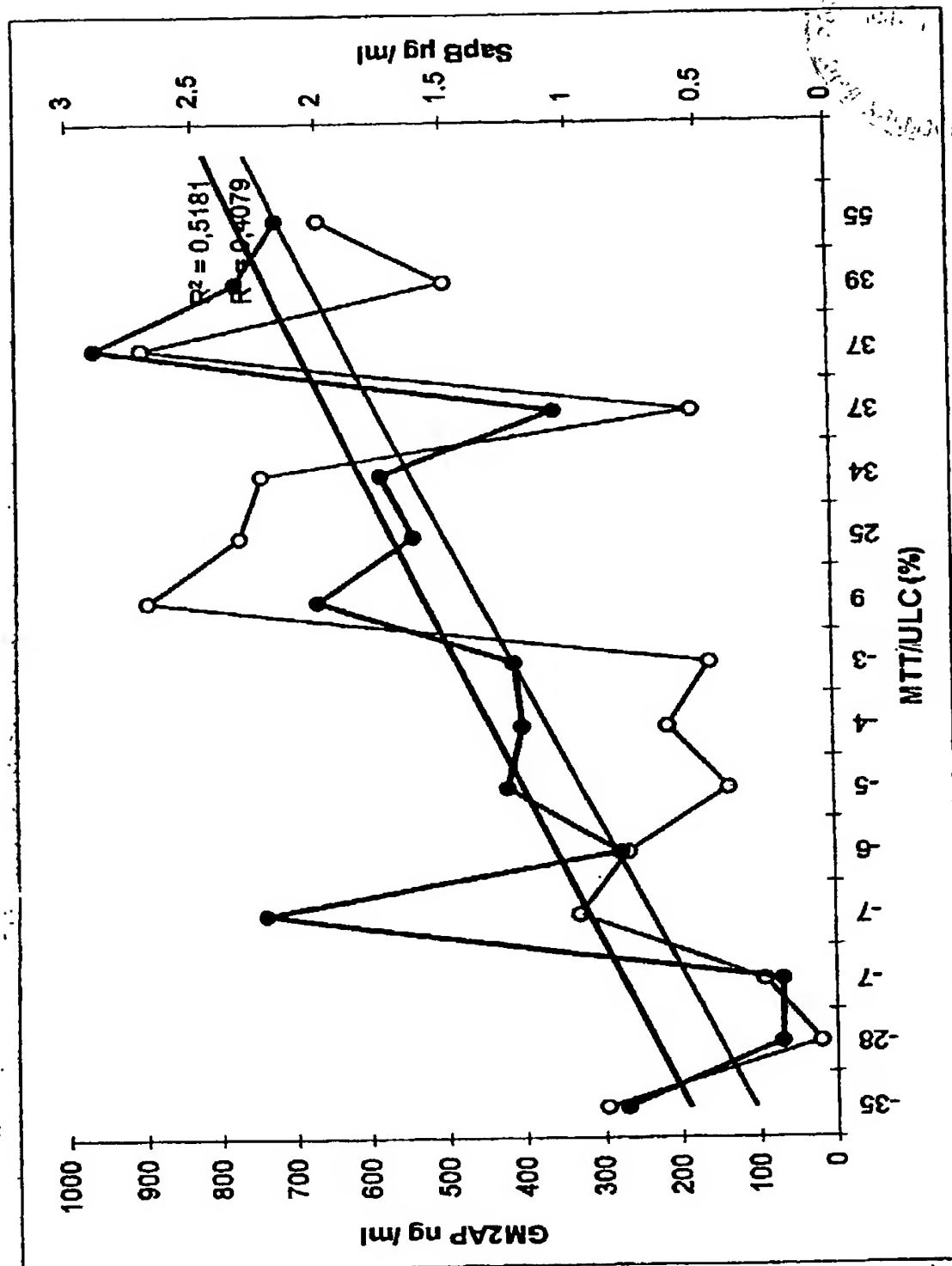


Figure 18



**DECLARATION AND POWER OF ATTORNEY
UNDER 35 USC §371(c)(4) FOR
PCT APPLICATION FOR UNITED STATES PATENT**

As a below named inventor, I hereby declare that:
my residence, post office address and citizenship are as stated below under my name;

I verily believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought, namely the invention entitled: USE OF A POLYPEPTIDE FOR DETECTING, PREVENTING OR TREATING A PATHOLOGICAL CONDITION ASSOCIATED WITH A DEGENERATIVE, NEUROLOGICAL OR AUTOIMMUNE DISEASE

described and claimed in international application number PCT/FR00/02057 filed July 17, 2000.

I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations §1.56.

Under Title 35, U.S. Code §119, the priority benefits of the following foreign application(s) filed by me or my legal representatives or assigns within one year prior to my international application are hereby claimed:

French Patent Application No. 99 09372 filed July 15, 1999.

The following application(s) for patent or inventor's certificate on this invention were filed in countries foreign to the United States of America either (a) more than one year prior to my international application, or (b) before the filing date of the above-named foreign priority application(s):

I hereby appoint the following as my attorneys of record with full power of substitution and revocation to prosecute this application and to transact all business in the Patent Office:

James A. Oliff, Reg. No. 27,075; William P. Berridge, Reg. No. 30,024;
Kirk M. Hudson, Reg. No. 27,562; Thomas J. Pardini, Reg. No. 30,411;
Edward P. Walker, Reg. No. 31,450; Robert A. Miller, Reg. No. 32,771;
Mario A. Costantino, Reg. No. 33,565; Stephen J. Roe, Reg. No. 34,463;
Joel S. Armstrong, Reg. No. 36,430; Christopher W. Brown, Reg. No. 38,025;
Richard E. Rice, Reg. No. 31,560; and Paul Tsou, Reg. No. 37,956.

ALL CORRESPONDENCE IN CONNECTION WITH THIS APPLICATION SHOULD BE SENT TO OLIFF & BERRIDGE, PLC, P.O. BOX 19928, ALEXANDRIA, VIRGINIA 22320, TELEPHONE (703) 836-6400.

I hereby declare that I have reviewed and understand the contents of this Declaration, and that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1	<i>Typewritten Full Name of Sole or First Inventor</i>	<u>Dominique</u> <u>ROECKLIN</u>		
		Given Name	Middle Initial	Family Name
2	Inventor's Signature:	<u>Dominique Roecklin</u>		
3	Date of Signature:	<u>March 19 2002</u>		
		Month	Day	Year
	Residence:	<u>Niederschaeffolsheim</u> <u>FRX</u> <u>FRANCE</u>		
		City	State or Province	Country
	Citizenship:	<u>FRANCE</u>		
	Post Office Address: (Insert complete mailing address, including country)	<u>14 rue de la Paix</u> <u>F-67500 Niederschaeffolsheim FRANCE</u>		

Note to Inventor: Please sign name on line 2 exactly as it appears in line 1 and insert the actual date of signing on line 3.

IF THERE IS MORE THAN ONE INVENTOR USE PAGE 2 AND PLACE AN "X" HERE ☒

(Discard this page in a sole inventor application)

10030937 092402

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Given Name Middle Initial Family Name
2 Inventor's Signature: *Hanno J. Kolbe*
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Month Day Year
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City State or Province Country
Citizenship: ~~FRANCE~~ GERMANY
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3 Date of Signature: March 1st 2002
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Citizenship: FRANCE
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Given Name Middle Initial Family Name
2 Inventor's Signature: *Carine*
3 Date of Signature: March 4th 2002
Month Day Year
Residence: Brignais FRX FRANCE
City State or Province Country
Citizenship: FRANCE
Post Office Address: 9 rue des Ronzières
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2 Inventor's Signature: *Lyse Santoro*
3 Date of Signature: 13/02/02
Month Day Year
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Citizenship: FRANCE
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1 Typewritten Full Name of Joint Inventor 6-00 Hervé Perron
Given Name Middle Initial Family Name
2 Inventor's Signature: *Hervé Perron*
3 Date of Signature: Feb 13th 2002
Month Day Year
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Note to Inventor: Please sign name on line 2 exactly as it appears in line 1 and insert the actual date of signing on line 3.
This form may be executed only when attached to the first page of the Declaration and Power of Attorney of the application to which it pertains.

10/030937

SEQUENCE LISTING

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KOLBE, Hanno

CHARLES, Marie-Helene

MALCUS, Carine

SANTORO, Lyse

PERRON, Herve

<120> USE OF A POLYPEPTIDE FOR DETECTING, PREVENTING OR TREATING A
 PATHOLOGICAL CONDITION ASSOCIATED WITH A DEGENERATIVE, NEUROLOGICAL OR
 AUTOIMMUNE DISEASE

<130> 111664

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<141> 2002-01-15

<150> PCT/FR00/02057

<151> 2000-07-17

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Val	Ile	Pro	Gly	Pro	Ile	Pro	Pro	Val	Arg	Ile	Glu	Ser	Ser	Ser	Ser	2245	2250	2255	
Thr	Val	Ala	Glu	Gly	Gln	Thr	Leu	Asp	Leu	Ser	Cys	Val	Val	Ala	Gly	2260	2265	2270	
Gln	Ala	His	Ala	Gln	Val	Thr	Trp	Tyr	Lys	Arg	Gly	Gly	Ser	Leu	Pro	2275	2280	2285	
Ala	Arg	His	Gln	Val	Arg	Gly	Ser	Arg	Leu	Tyr	Ile	Phe	Gln	Ala	Ser	2290	2295	2300	
Pro	Ala	Asp	Ala	Gly	Gln	Tyr	Val	Cys	Arg	Ala	Ser	Asn	Gly	Met	Glu	2305	2310	2315	2320
Ala	Ser	Ile	Thr	Val	Thr	Val	Thr	Gly	Thr	Gln	Gly	Ala	Asn	Leu	Ala	2325	2330	2335	
Tyr	Pro	Ala	Gly	Ser	Thr	Gln	Pro	Ile	Arg	Ile	Glu	Pro	Ser	Ser	Ser	2340	2345	2350	
Gln	Val	Ala	Glu	Gly	Gln	Thr	Leu	Asp	Leu	Asn	Cys	Val	Val	Pro	Gly	2355	2360	2365	
Gln	Ser	His	Ala	Gln	Val	Thr	Trp	His	Lys	Arg	Gly	Gly	Ser	Leu	Pro	2370	2375	2380	

Val Arg His Gln Thr His Gly Ser Leu Leu Arg Leu Tyr Gln Ala Ser
 2385 2390 2395 2400

Pro Ala Asp Ser Gly Glu Tyr Val Cys Arg Val Leu Gly Ser Ser Val
 2405 2410 2415

Pro Leu Glu Ala Ser Val Leu Val Thr Ile Glu Pro Ala Gly Ser Val
 2420 2425 2430

Pro Ala Leu Gly Val Thr Pro Thr Val Arg Ile Glu Ser Ser Ser Ser
 2435 2440 2445

Gln Val Ala Glu Gly Gln Thr Leu Asp Leu Asn Cys Leu Val Ala Gly
 2450 2455 2460

Gln Ala His Ala Gln Val Thr Trp His Lys Arg Gly Gly Ser Leu Pro
 2465 2470 2475 2480

Ala Arg His Gln Val His Gly Ser Arg Leu Arg Leu Leu Gln Val Thr
 2485 2490 2495

Pro Ala Asp Ser Gly Glu Tyr Val Cys Arg Val Val Gly Ser Ser Gly
 2500 2505 2510

Thr Gln Glu Ala Ser Val Leu Val Thr Ile Gln Gln Arg Leu Ser Gly
 2515 2520 2525

Ser His Ser Gln Gly Val Ala Tyr Pro Val Arg Ile Glu Ser Ser Ser
 2530 2535 2540

Ala Ser Leu Ala Asn Gly His Thr Leu Asp Leu Asn Cys Leu Val Ala
 2545 2550 2555 2560

Ser Gln Ala Pro His Thr Ile Thr Trp Tyr Lys Arg Gly Gly Ser Leu
 2565 2570 2575

Pro Ser Arg His Gln Ile Val Gly Ser Arg Leu Arg Ile Pro Gln Val
 2580 2585 2590

Thr Pro Ala Asp Ser Gly Glu Tyr Val Cys His Val Ser Asn Gly Ala
 2595 2600 2605

Gly Ser Arg Glu Thr Ser Leu Ile Val Thr Ile Gln Gly Ser Gly Ser
 2610 2615 2620

Ser His Val Pro Arg Val Ser Pro Pro Ile Arg Ile Glu Ser Ser Ser
 2625 2630 2635 2640

Pro Thr Val Val Glu Gly Gln Thr Leu Asp Leu Asn Cys Val Val Ala
 2645 2650 2655

Arg Gln Pro Gln Ala Ile Ile Thr Trp Tyr Lys Arg Gly Gly Ser Leu
 2660 2665 2670

Pro Ser Arg His Gln Thr His Gly Ser His Leu Arg Leu His Gln Met
 2675 2680 2685

Ser Val Ala Asp Ser Gly Glu Tyr Val Cys Arg Ala Asn Asn Asn Ile
 2690 2695 2700

Asp Ala Leu Glu Ala Ser Ile Val Ile Ser Val Ser Pro Ser Ala Gly

2705		2710		2715		2720
Ser Pro Ser Ala Pro Gly Ser Ser Met Pro Ile Arg Ile Glu Ser Ser						
	2725			2730		2735
Ser Ser His Val Ala Glu Gly Glu Thr Leu Asp Leu Asn Cys Val Val						
	2740			2745		2750
Pro Gly Gln Ala His Ala Gln Val Thr Trp His Lys Arg Gly Gly Ser						
	2755			2760		2765
Leu Pro Ser Tyr His Gln Thr Arg Gly Ser Arg Leu Arg Leu His His						
	2770			2775		2780
Val Ser Pro Ala Asp Ser Gly Glu Tyr Val Cys Arg Val Met Gly Ser						
	2785			2790		2795
Ser Gly Pro Leu Glu Ala Ser Val Leu Val Thr Ile Glu Ala Ser Gly						
	2805			2810		2815
Ser Ser Ala Val His Val Pro Ala Pro Gly Gly Ala Pro Pro Ile Arg						
	2820			2825		2830
Ile Glu Pro Ser Ser Ser Arg Val Ala Glu Gly Gln Thr Leu Asp Leu						
	2835			2840		2845
Lys Cys Val Val Pro Gly Gln Ala His Ala Gln Val Thr Trp His Lys						
	2850			2855		2860
Arg Gly Gly Asn Leu Pro Ala Arg His Gln Val His Gly Pro Leu Leu						
	2865			2870		2875
Arg Leu Asn Gln Val Ser Pro Ala Asp Ser Gly Glu Tyr Ser Cys Gln						
	2885			2890		2895
Val Thr Gly Ser Ser Gly Thr Leu Glu Ala Ser Val Leu Val Thr Ile						
	2900			2905		2910
Glu Pro Ser Ser Pro Gly Pro Ile Pro Ala Pro Gly Leu Ala Gln Pro						
	2915			2920		2925
Ile Tyr Ile Glu Ala Ser Ser Ser His Val Thr Glu Gly Gln Thr Leu						
	2930			2935		2940
Asp Leu Asn Cys Val Val Pro Gly Gln Ala His Ala Gln Val Thr Trp						
	2945			2950		2955
Tyr Lys Arg Gly Gly Ser Leu Pro Ala Arg His Gln Thr His Gly Ser						
	2965			2970		2975
Gln Leu Arg Leu His His Val Ser Pro Ala Asp Ser Gly Glu Tyr Val						
	2980			2985		2990
Cys Arg Ala Ala Gly Gly Pro Gly Pro Glu Gln Glu Ala Ser Phe Thr						
	2995			3000		3005
Val Thr Val Pro Pro Ser Glu Gly Ser Ser Tyr Arg Leu Arg Ser Pro						
	3010			3015		3020
Val Ile Ser Ile Asp Pro Pro Ser Ser Thr Val Gln Gln Gly Gln Asp						
	3025			3030		3035
						3040

Ala Ser Phe Lys Cys Leu Ile His Asp Gly Ala Ala Pro Ile Ser Leu
3045 3050 3055

Glu Trp Lys Thr Arg Asn Gln Glu Leu Glu Asp Asn Val His Ile Ser
3060 3065 3070

Pro Asn Gly Ser Ile Ile Thr Ile Val Gly Thr Arg Pro Ser Asn His
3075 3080 3085

Gly Thr Tyr Arg Cys Val Ala Ser Asn Ala Tyr Gly Val Ala Gln Ser
3090 3095 3100

Val Val Asn Leu Ser Val His Gly Pro Pro Thr Val Ser Val Leu Pro
3105 3110 3115 3120

Glu Gly Pro Val Trp Val Lys Val Gly Lys Ala Val Thr Leu Glu Cys
3125 3130 3135

Val Ser Ala Gly Glu Pro Arg Ser Ser Ala Arg Trp Thr Arg Ile Ser
3140 3145 3150

Ser Thr Pro Ala Lys Leu Glu Gln Arg Thr Tyr Gly Leu Met Asp Ser
3155 3160 3165

His Thr Val Leu Gln Ile Ser Ser Ala Lys Pro Ser Asp Ala Gly Thr
3170 3175 3180

Tyr Val Cys Leu Ala Gln Asn Ala Leu Gly Thr Ala Gln Lys Gln Val
3185 3190 3195 3200

Glu Val Ile Val Asp Thr Gly Ala Met Ala Pro Gly Ala Pro Gln Val
3205 3210 3215

Gln Ala Glu Glu Ala Glu Leu Thr Val Glu Ala Gly His Thr Ala Thr
3220 3225 3230

Leu Arg Cys Ser Ala Thr Gly Ser Pro Ala Arg Thr Ile His Trp Ser
3235 3240 3245

Lys Leu Arg Ser Pro Leu Pro Trp Gln His Arg Leu Glu Gly Asp Thr
3250 3255 3260

Leu Ile Ile Pro Arg Val Ala Gln Gln Asp Ser Gly Gln Tyr Ile Cys
3265 3270 3275 3280

Asn Ala Thr Ser Pro Ala Gly His Ala Glu Ala Thr Ile Ile Leu His
3285 3290 3295

Val Glu Ser Pro Pro Tyr Ala Thr Thr Val Pro Glu His Ala Ser Val
3300 3305 3310

Gln Ala Gly Glu Thr Val Gln Leu Gln Cys Leu Ala His Gly Thr Pro
3315 3320 3325

Pro Leu Thr Phe Gln Trp Ser Arg Val Gly Ser Ser Leu Pro Gly Arg
3330 3335 3340

Ala Thr Ala Arg Asn Glu Leu Leu His Phe Glu Arg Ala Ala Pro Glu
3345 3350 3355 3360

Asp Ser Gly Arg Tyr Arg Cys Arg Val Thr Asn Lys Val Gly Ser Ala
 3365 3370 3375
 Glu Ala Phe Ala Gln Leu Leu Val Gln Gly Pro Pro Gly Ser Leu Pro
 3380 3385 3390
 Ala Thr Ser Ile Pro Ala Gly Ser Thr Pro Thr Val Gln Val Thr Pro
 3395 3400 3405
 Gln Leu Glu Thr Lys Ser Ile Gly Ala Ser Val Glu Phe His Cys Ala
 3410 3415 3420
 Val Pro Ser Asp Arg Gly Thr Gln Leu Arg Trp Phe Lys Glu Gly Gly
 3425 3430 3435 3440
 Gln Leu Pro Pro Gly His Ser Val Gln Asp Gly Val Leu Arg Ile Gln
 3445 3450 3455
 Asn Leu Asp Gln Ser Cys Gln Gly Thr Tyr Ile Cys Gln Ala His Gly
 3460 3465 3470
 Pro Trp Gly Lys Ala Gln Ala Ser Ala Gln Leu Val Ile Gln Ala Leu
 3475 3480 3485
 Pro Ser Val Leu Ile Asn Ile Arg Thr Ser Val Gln Thr Val Val Val
 3490 3495 3500
 Gly His Ala Val Glu Phe Glu Cys Leu Ala Leu Gly Asp Pro Lys Pro
 3505 3510 3515 3520
 Gln Val Thr Trp Ser Lys Val Gly Gly His Leu Arg Pro Gly Ile Val
 3525 3530 3535
 Gln Ser Gly Gly Val Val Arg Ile Ala His Val Glu Leu Ala Asp Ala
 3540 3545 3550
 Gly Gln Tyr Arg Cys Thr Ala Thr Asn Ala Ala Gly Thr Thr Gln Ser
 3555 3560 3565
 His Val Leu Leu Leu Val Gln Ala Leu Pro Gln Ile Ser Met Pro Gln
 3570 3575 3580
 Glu Val Arg Val Pro Ala Gly Ser Ala Ala Val Phe Pro Cys Ile Ala
 3585 3590 3595 3600
 Ser Gly Tyr Pro Thr Pro Asp Ile Ser Trp Ser Lys Leu Asp Gly Ser
 3605 3610 3615
 Leu Pro Pro Asp Ser Arg Leu Glu Asn Asn Met Leu Met Leu Pro Ser
 3620 3625 3630
 Val Gln Pro Gln Asp Ala Gly Thr Tyr Val Cys Thr Ala Thr Asn Arg
 3635 3640 3645
 Gln Gly Lys Val Lys Ala Phe Ala His Leu Gln Val Pro Glu Arg Val
 3650 3655 3660
 Val Pro Tyr Phe Thr Gln Thr Pro Tyr Ser Phe Leu Pro Leu Pro Thr
 3665 3670 3675 3680
 Ile Lys Asp Ala Tyr Arg Lys Phe Glu Ile Lys Ile Thr Phe Arg Pro

3685	3690	3695
Asp Ser Ala Asp Gly Met Leu Leu Tyr Asn Gly Gln Lys Arg Val Pro		
3700	3705	3710
Gly Ser Pro Thr Asn Leu Ala Asn Arg Gln Pro Asp Phe Ile Ser Phe		
3715	3720	3725
Gly Leu Val Gly Gly Arg Pro Glu Phe Arg Phe Asp Ala Gly Ser Gly		
3730	3735	3740
Met Ala Thr Ile Arg His Pro Thr Pro Leu Ala Leu Gly His Phe His		
3745	3750	3755
Thr Val Thr Leu Leu Arg Ser Leu Thr Gln Gly Ser Leu Ile Val Gly		
3765	3770	3775
Asp Leu Ala Pro Val Asn Gly Thr Ser Gln Gly Lys Phe Gln Gly Leu		
3780	3785	3790
Asp Leu Asn Glu Glu Leu Tyr Leu Gly Gly Tyr Pro Asp Tyr Gly Ala		
3795	3800	3805
Ile Pro Lys Ala Gly Leu Ser Ser Gly Phe Ile Gly Cys Val Arg Glu		
3810	3815	3820
Leu Arg Ile Gln Gly Glu Glu Ile Val Phe His Asp Leu Asn Leu Thr		
3825	3830	3835
Ala His Gly Ile Ser His Cys Pro Thr Cys Arg Asp Arg Pro Cys Gln		
3845	3850	3855
Asn Gly Gly Gln Cys His Asp Ser Glu Ser Ser Ser Tyr Val Cys Val		
3860	3865	3870
Cys Pro Ala Gly Phe Thr Gly Ser Arg Cys Glu His Ser Gln Ala Leu		
3875	3880	3885
His Cys His Pro Glu Ala Cys Gly Pro Asp Ala Thr Cys Val Asn Arg		
3890	3895	3900
Pro Asp Gly Arg Gly Tyr Thr Cys Arg Cys His Leu Gly Arg Ser Gly		
3905	3910	3915
Leu Arg Cys Glu Glu Gly Val Thr Val Thr Thr Pro Ser Leu Ser Gly		
3925	3930	3935
Ala Gly Ser Tyr Leu Ala Leu Pro Ala Leu Thr Asn Thr His His Glu		
3940	3945	3950
Leu Arg Leu Asp Val Glu Phe Lys Pro Leu Ala Pro Asp Gly Val Leu		
3955	3960	3965
Leu Phe Ser Gly Gly Lys Ser Gly Pro Val Glu Asp Phe Val Ser Leu		
3970	3975	3980
Ala Met Val Gly Gly His Leu Glu Phe Arg Tyr Glu Leu Gly Ser Gly		
3985	3990	3995
Leu Ala Val Leu Arg Thr Ala Glu Pro Leu Ala Leu Gly Arg Trp His		
4005	4010	4015

Arg Val Ser Ala Glu Arg Leu Asn Lys Asp Gly Ser Leu Arg Val Asn
 4020 4025 4030
 Gly Gly Arg Pro Val Leu Arg Ser Ser Pro Gly Lys Ser Gln Gly Leu
 4035 4040 4045
 Asn Leu His Thr Leu Leu Tyr Leu Gly Gly Val Glu Pro Ser Val Pro
 4050 4055 4060
 Leu Ser Pro Ala Thr Asn Met Ser Ala His Phe Arg Gly Cys Val Gly
 4065 4070 4075 4080
 Glu Val Ser Val Asn Gly Lys Arg Leu Asp Leu Thr Tyr Ser Phe Leu
 4085 4090 4095
 Gly Ser Gln Gly Ile Gly Gln Cys Tyr Asp Ser Ser Pro Cys Glu Arg
 4100 4105 4110
 Gln Pro Cys Gln His Gly Ala Thr Cys Met Pro Ala Gly Glu Tyr Glu
 4115 4120 4125
 Phe Gln Cys Leu Cys Arg Asp Gly Ile Lys Gly Asp Leu Cys Glu His
 4130 4135 4140
 Glu Glu Asn Pro Cys Gln Leu Arg Glu Pro Cys Leu His Gly Gly Thr
 4145 4150 4155 4160
 Cys Gln Gly Thr Arg Cys Leu Cys Leu Pro Gly Phe Ser Gly Pro Arg
 4165 4170 4175
 Cys Gln Gln Gly Ser Gly His Gly Ile Ala Glu Ser Asp Trp His Leu
 4180 4185 4190
 Glu Gly Ser Gly Gly Asn Asp Ala Pro Gly Gln Tyr Gly Ala Tyr Phe
 4195 4200 4205
 His Asp Asp Gly Phe Leu Ala Phe Pro Gly His Val Phe Ser Arg Ser
 4210 4215 4220
 Leu Pro Glu Val Pro Glu Thr Ile Glu Leu Glu Val Arg Thr Ser Thr
 4225 4230 4235 4240
 Ala Ser Gly Leu Leu Leu Trp Gln Gly Val Glu Val Gly Glu Ala Gly
 4245 4250 4255
 Gln Gly Lys Asp Phe Ile Ser Leu Gly Leu Gln Asp Gly His Leu Val
 4260 4265 4270
 Phe Arg Tyr Gln Leu Gly Ser Gly Glu Ala Arg Leu Val Ser Glu Asp
 4275 4280 4285
 Pro Ile Asn Asp Gly Glu Trp His Arg Val Thr Ala Leu Arg Glu Gly
 4290 4295 4300
 Arg Arg Gly Ser Ile Gln Val Asp Gly Glu Glu Leu Val Ser Gly Arg
 4305 4310 4315 4320
 Ser Pro Gly Pro Asn Val Ala Val Asn Ala Lys Gly Ser Ile Tyr Ile
 4325 4330 4335

Gly Gly Ala Pro Asp Val Ala Thr Leu Thr Gly Gly Arg Phe Ser Ser
4340 4345 4350

Gly Ile Thr Gly Cys Val Lys Asn Leu Val Leu His Ser Ala Arg Pro
4355 4360 4365

Gly Ala Pro Pro Pro Gln Pro Leu Asp Leu Gln His Arg Ala Gln Ala
4370 4375 4380

Gly Ala Asn Thr Arg Pro Cys Pro Ser
4385 4390

<210> 2
<211> 195
<212> PRT
<213> Homo sapiens

<400> 2
Asp Ala Pro Gly Gln Tyr Gly Ala Tyr Phe His Asp Asp Gly Phe Leu
1 5 10 15

Ala Phe Pro Gly His Val Phe Ser Arg Ser Leu Pro Glu Val Pro Glu
20 25 30

Thr Ile Glu Leu Glu Val Arg Thr Ser Thr Ala Ser Gly Leu Leu Leu
35 40 45

Trp Gln Gly Val Glu Val Gly Glu Ala Gly Gln Gly Lys Asp Phe Ile
50 55 60

Ser Leu Gly Leu Gln Asp Gly His Leu Val Phe Arg Tyr Gln Leu Gly
65 70 75 80

Ser Gly Glu Ala Arg Leu Val Ser Glu Asp Pro Ile Asn Asp Gly Glu
85 90 95

Trp His Arg Val Thr Ala Leu Arg Glu Gly Arg Arg Gly Ser Ile Gln
100 105 110

Val Asp Gly Glu Glu Leu Val Ser Gly Arg Ser Pro Gly Pro Asn Val
115 120 125

Ala Val Asn Ala Lys Gly Ser Val Tyr Ile Gly Gly Ala Pro Asp Val
130 135 140

Ala Thr Leu Thr Gly Gly Arg Phe Ser Ser Gly Ile Thr Gly Cys Val
145 150 155 160

Lys Asn Leu Val Leu His Ser Ala Arg Pro Gly Ala Pro Pro Pro Gln
165 170 175

Pro Leu Asp Leu Gln His Arg Ala Gln Ala Gly Ala Asn Thr Arg Pro
180 185 190

Cys Pro Ser
195

<210> 3
<211> 508

<212> PRT

<213> Homo sapiens

<400> 3

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Arg Thr Cys Arg Cys Lys Asn Asn Val Val Gly Arg Leu Cys Asn Glu
 1          5          10          15

Cys Ala Asp Arg Ser Phe His Leu Ser Thr Arg Asn Pro Asp Gly Cys
          20          25          30

Leu Lys Cys Phe Cys Met Gly Val Ser Arg His Cys Thr Ser Ser Ser
          35          40          45

Trp Ser Arg Ala Gln Leu His Gly Ala Ser Glu Glu Pro Gly His Phe
          50          55          60

Ser Leu Thr Asn Ala Ala Ser Thr His Thr Thr Asn Glu Gly Ile Phe
          65          70          75          80

Ser Pro Thr Pro Gly Glu Leu Gly Phe Ser Ser Phe His Arg Leu Leu
          85          90          95

Ser Gly Pro Tyr Phe Trp Ser Leu Pro Ser Arg Phe Leu Gly Asp Lys
          100          105          110

Val Thr Ser Tyr Gly Gly Glu Leu Arg Phe Thr Val Thr Gln Arg Ser
          115          120          125

Gln Pro Gly Ser Thr Pro Leu His Gly Gln Pro Leu Val Val Leu Gln
          130          135          140

Gly Asn Asn Ile Ile Leu Glu His His Val Ala Gln Glu Pro Ser Pro
          145          150          155          160

Gly Gln Pro Ser Thr Phe Ile Val Pro Phe Arg Glu Gln Ala Trp Gln
          165          170          175

Arg Pro Asp Gly Gln Pro Ala Thr Arg Glu His Leu Leu Met Ala Leu
          180          185          190

Ala Gly Ile Asp Thr Leu Leu Ile Arg Ala Ser Tyr Ala Gln Gln Pro
          195          200          205

Ala Glu Ser Arg Leu Ser Gly Ile Ser Met Asp Val Ala Val Pro Glu
          210          215          220

Glu Thr Gly Gln Asp Pro Ala Leu Glu Val Glu Gln Cys Ser Cys Pro
          225          230          235          240

Pro Gly Tyr Leu Gly Pro Ser Cys Gln Asp Cys Asp Thr Gly Tyr Thr
          245          250          255

Arg Thr Pro Ser Gly Leu Tyr Leu Gly Thr Cys Glu Arg Cys Ser Cys
          260          265          270

His Gly His Ser Glu Ala Cys Glu Pro Glu Thr Gly Ala Cys Gln Gly
          275          280          285

Cys Gln His His Thr Glu Gly Pro Arg Cys Glu Gln Cys Gln Pro Gly
          290          295          300

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Tyr Tyr Gly Asp Ala Gln Arg Gly Thr Pro Gln Asp Cys Gln Leu Cys
 305 310 315 320
 Pro Cys Tyr Gly Asp Pro Ala Ala Gly Gln Ala Ala Leu Thr Cys Phe
 325 330 335
 Leu Asp Thr Asp Gly His Pro Thr Cys Asp Ala Cys Ser Pro Gly His
 340 345 350
 Ser Gly Arg His Cys Glu Arg Cys Ala Pro Gly Tyr Tyr Gly Asn Pro
 355 360 365
 Ser Gln Gly Gln Pro Cys Gln Arg Asp Ser Gln Val Pro Gly Pro Ile
 370 375 380
 Gly Cys Asn Cys Asp Pro Gln Gly Ser Val Ser Ser Gln Cys Asp Ala
 385 390 395 400
 Ala Gly Gln Cys Gln Cys Lys Ala Gln Val Glu Gly Leu Thr Cys Ser
 405 410 415
 His Cys Arg Pro His His Phe His Leu Ser Ala Ser Asn Pro Asp Gly
 420 425 430
 Cys Leu Pro Cys Phe Cys Met Gly Ile Thr Gln Gln Cys Ala Ser Ser
 435 440 445
 Ala Tyr Thr Arg His Leu Ile Ser Thr His Phe Ala Pro Gly Asp Phe
 450 455 460
 Gln Gly Phe Ala Leu Val Asn Pro Gln Arg Asn Ser Arg Leu Thr Gly
 465 470 475 480
 Glu Phe Thr Val Glu Pro Val Pro Glu Gly Ala Gln Leu Ser Phe Gly
 485 490 495
 Asn Phe Ala Gln Leu Gly His Glu Ser Phe Tyr Trp
 500 505

<210> 4
 <211> 199
 <212> PRT
 <213> Homo sapiens

<400> 4
 Met Lys Trp Val Trp Ala Leu Leu Leu Leu Ala Ala Trp Ala Ala Ala
 1 5 10 15
 Glu Arg Asp Cys Arg Val Ser Ser Phe Arg Val Lys Glu Asn Phe Asp
 20 25 30
 Lys Ala Arg Phe Ser Gly Thr Trp Tyr Ala Met Ala Lys Lys Asp Pro
 35 40 45
 Glu Gly Leu Phe Leu Gln Asp Asn Ile Val Ala Glu Phe Ser Val Asp
 50 55 60
 Glu Thr Gly Gln Met Ser Ala Thr Ala Lys Gly Arg Val Arg Leu Leu
 65 70 75 80

Asn Asn Trp Asp Val Cys Ala Asp Met Val Gly Thr Phe Thr Asp Thr
85 90 95

Glu Asp Pro Ala Lys Phe Lys Met Lys Tyr Trp Gly Val Ala Ser Phe
100 105 110

Leu Gln Lys Gly Asn Asp Asp His Trp Ile Val Asp Thr Asp Tyr Asp
115 120 125

Thr Tyr Ala Val Gln Tyr Ser Cys Arg Leu Leu Asn Leu Asp Gly Thr
130 135 140

Cys Ala Asp Ser Tyr Ser Phe Val Phe Ser Arg Asp Pro Asn Gly Leu
145 150 155 160

Pro Pro Glu Ala Gln Lys Ile Val Arg Gln Arg Gln Glu Glu Leu Cys
165 170 175

Leu Ala Arg Gln Tyr Arg Leu Ile Val His Asn Gly Tyr Cys Asp Gly
180 185 190

Arg Ser Glu Arg Asn Leu Leu
195

<210> 5
<211> 199
<212> PRT
<213> Homo sapiens

<400> 5
Met Lys Trp Val Trp Ala Leu Leu Leu Leu Ala Ala Trp Ala Ala Ala
1 5 10 15

Glu Arg Asp Cys Arg Val Ser Ser Phe Arg Val Lys Glu Asn Phe Asp
20 25 30

Lys Ala Arg Phe Ser Gly Thr Trp Tyr Ala Met Ala Lys Lys Asp Pro
35 40 45

Glu Gly Leu Phe Leu Gln Asp Asn Ile Val Ala Glu Phe Ser Val Asp
50 55 60

Glu Thr Gly Gln Met Ser Ala Thr Ala Lys Gly Arg Val Arg Leu Leu
65 70 75 80

Asn Asn Trp Asp Val Cys Ala Asp Met Val Gly Thr Phe Thr Asp Thr
85 90 95

Glu Asp Pro Ala Lys Phe Lys Met Lys Tyr Trp Gly Val Ala Ser Phe
100 105 110

Leu Gln Lys Gly Asn Asp Asp His Trp Ile Val Asp Thr Asp Tyr Asp
115 120 125

Thr Tyr Ala Val Gln Tyr Ser Cys Arg Leu Leu Asn Leu Asp Gly Thr
130 135 140

Cys Ala Asp Ser Tyr Ser Phe Val Phe Ser Arg Asp Pro Asn Gly Leu
145 150 155 160

<400> 7

Glu	Arg	Asp	Cys	Arg	Val	Ser	Ser	Phe	Arg	Val	Lys	Glu	Asn	Phe	Asp
1				5					10					15	
Lys	Ala	Arg	Phe	Ser	Gly	Thr	Trp	Tyr	Ala	Met	Ala	Lys	Lys	Asp	Pro
			20					25						30	
Glu	Gly	Leu	Phe	Leu	Gln	Asp	Asn	Ile	Val	Ala	Glu	Phe	Ser	Val	Asp
		35					40					45			
Glu	Thr	Gly	Gln	Met	Ser	Ala	Thr	Ala	Lys	Gly	Arg	Val	Arg	Leu	Leu
	50					55					60				
Asn	Asn	Trp	Asp	Val	Cys	Ala	Asp	Met	Val	Gly	Thr	Phe	Thr	Asp	Thr
65					70					75					80
Glu	Asp	Pro	Ala	Lys	Phe	Lys	Met	Lys	Tyr	Trp	Gly	Val	Ala	Ser	Phe
				85					90					95	
Leu	Gln	Lys	Gly	Asn	Asp	Asp	His	Trp	Ile	Val	Asp	Thr	Asp	Tyr	Asp
			100					105					110		
Thr	Tyr	Ala	Val	Gln	Tyr	Ser	Cys	Arg	Leu	Leu	Asn	Leu	Asp	Gly	Thr
		115					120					125			
Cys	Ala	Asp	Ser	Tyr	Ser	Phe	Val	Phe	Ser	Arg	Asp	Pro	Asn	Gly	Leu
	130					135					140				
Pro	Pro	Glu	Ala	Gln	Lys	Ile	Val	Arg	Gln	Arg	Gln	Glu	Glu	Leu	Cys
145					150					155					160
Leu	Ala	Arg	Gln	Tyr	Arg	Leu	Ile	Val	His	Asn	Gly	Tyr	Cys	Asp	Gly
			165						170					175	
Arg	Ser	Glu	Arg	Asn	Leu										
			180												

<210> 8

<211> 193

<212> PRT

<213> Homo sapiens

<400> 8

Met	Gln	Ser	Leu	Met	Gln	Ala	Pro	Leu	Leu	Ile	Ala	Leu	Gly	Leu	Leu
1				5					10					15	
Leu	Ala	Thr	Pro	Ala	Gln	Ala	His	Leu	Lys	Lys	Pro	Ser	Gln	Leu	Ser
			20					25					30		
Ser	Phe	Ser	Trp	Asp	Asn	Cys	Asp	Glu	Gly	Lys	Asp	Pro	Ala	Val	Ile
		35				40						45			
Arg	Ser	Leu	Thr	Leu	Glu	Pro	Asp	Pro	Ile	Val	Val	Pro	Gly	Asn	Val
	50					55					60				
Thr	Leu	Ser	Val	Val	Gly	Ser	Thr	Ser	Val	Pro	Leu	Ser	Ser	Pro	Leu
65					70					75					80
Lys	Val	Asp	Leu	Val	Leu	Glu	Lys	Glu	Val	Ala	Gly	Leu	Trp	Ile	Lys
			85						90					95	

Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys
100 105 110

Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro
115 120 125

Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr
130 135 140

Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro
145 150 155 160

Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser
165 170 175

Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly
180 185 190

Ile

<210> 9
<211> 193
<212> PRT
<213> Homo sapiens

<400> 9
Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu
1 5 10 15

Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser
20 25 30

Ser Phe Ser Trp Asp Asn Cys Phe Glu Gly Lys Asp Pro Ala Val Ile
35 40 45

Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val
50 55 60

Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu
65 70 75 80

Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys
85 90 95

Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys
100 105 110

Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro
115 120 125

Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr
130 135 140

Tyr Ser Leu Pro Lys Ser Glu Phe Ala Val Pro Asp Leu Glu Leu Pro
145 150 155 160

Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser
165 170 175

Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly
 180 185 190

Ile

<210> 10
 <211> 178
 <212> PRT
 <213> Homo sapiens

<400> 10
 Leu Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu
 1 5 10 15
 Ser Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val
 20 25 30
 Ile Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn
 35 40 45
 Val Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro
 50 55 60
 Leu Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile
 65 70 75 80
 Lys Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe
 85 90 95
 Cys Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu
 100 105 110
 Pro Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly
 115 120 125
 Thr Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu
 130 135 140
 Pro Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser
 145 150 155 160
 Ser Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys
 165 170 175

Gly Ile

<210> 11
 <211> 200
 <212> PRT
 <213> Homo sapiens

<400> 11
 Arg Ala Gly Pro Pro Phe Pro Met Gln Ser Leu Met Gln Ala Pro Leu
 1 5 10 15
 Leu Ile Ala Leu Gly Leu Leu Leu Ala Ala Pro Ala Gln Ala His Leu

20										25					30															
Lys	Lys	Pro	Ser	Gln	Leu	Ser	Ser	Phe	Ser	Trp	Asp	Asn	Cys	Asp	Glu															
		35					40					45																		
Gly	Lys	Asp	Pro	Ala	Val	Ile	Arg	Ser	Leu	Thr	Leu	Glu	Pro	Asp	Pro															
	50					55					60																			
Ile	Ile	Val	Pro	Gly	Asn	Val	Thr	Leu	Ser	Val	Met	Gly	Ser	Thr	Ser															
65					70					75					80															
Val	Pro	Leu	Ser	Ser	Pro	Leu	Lys	Val	Asp	Leu	Val	Leu	Glu	Lys	Glu															
				85					90					95																
Val	Ala	Gly	Leu	Trp	Ile	Lys	Ile	Pro	Cys	Thr	Asp	Tyr	Ile	Gly	Ser															
			100					105					110																	
Cys	Thr	Phe	Glu	His	Phe	Cys	Asp	Val	Leu	Asp	Met	Leu	Ile	Pro	Thr															
		115					120					125																		
Gly	Glu	Pro	Cys	Pro	Glu	Pro	Leu	Arg	Thr	Tyr	Gly	Leu	Pro	Cys	His															
	130					135					140																			
Cys	Pro	Phe	Lys	Glu	Gly	Thr	Tyr	Ser	Leu	Pro	Lys	Ser	Glu	Phe	Val															
145					150				155						160															
Val	Pro	Asp	Leu	Glu	Leu	Pro	Ser	Trp	Leu	Thr	Thr	Gly	Asn	Tyr	Arg															
				165				170						175																
Ile	Glu	Ser	Val	Leu	Ser	Ser	Ser	Gly	Lys	Arg	Leu	Gly	Cys	Ile	Lys															
			180					185					190																	
Ile	Ala	Ala	Ser	Leu	Lys	Gly	Ile																							
		195					200																							

<210> 12
 <211> 189
 <212> PRT
 <213> Homo sapiens

<400> 12
 Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu Leu Ala Thr Pro
 1 5 10 15
 Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser Ser Phe Ser Trp
 20 25 30
 Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile Arg Ser Leu Thr
 35 40 45
 Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val Thr Leu Ser Val
 50 55 60
 Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu Lys Val Asp Leu
 65 70 75 80
 Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys Ile Pro Cys Thr
 85 90 95
 Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys Asp Val Leu Asp

	100		105		110
Met	Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro Leu Arg Thr Tyr				
	115		120		125
Gly	Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr Tyr Ser Leu Pro				
	130		135		140
Lys	Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro Ser Trp Leu Thr				
	145		150		155 160
Thr	Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser Ser Gly Lys Arg				
		165		170	175
Leu	Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly Ile				
	180		185		

<210> 13
 <211> 193
 <212> PRT
 <213> Homo sapiens

<400> 13
Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu
1 5 10 15
Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser
20 25 30
Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile
35 40 45
Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val
50 55 60
Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu
65 70 75 80
Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys
85 90 95
Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys
100 105 110
Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro
115 120 125
Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr
130 135 140
Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro
145 150 155 160
Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser
165 170 175
Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly
180 185 190

Ile

<210> 14
 <211> 193
 <212> PRT
 <213> Homo sapiens

<400> 14
 Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu
 1 5 10 15
 Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser
 20 25 30
 Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile
 35 40 45
 Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val
 50 55 60
 Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu
 65 70 75 80
 Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys
 85 90 95
 Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys
 100 105 110
 Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro
 115 120 125
 Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr
 130 135 140
 Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro
 145 150 155 160
 Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser
 165 170 175
 Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly
 180 185 190
 Ile

<210> 15
 <211> 193
 <212> PRT
 <213> Homo sapiens

<400> 15
 Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu
 1 5 10 15
 Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser
 20 25 30

Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro
115 120 125

Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr
130 135 140

Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro
145 150 155 160

Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser
165 170 175

Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly
180 185 190

Ile

<210> 17
<211> 114
<212> PRT
<213> Homo sapiens

<400> 17
Met Thr Cys Lys Met Ser Gln Leu Glu Arg Asn Ile Glu Thr Ile Ile
1 5 10 15

Asn Thr Phe His Gln Tyr Ser Val Lys Leu Gly His Pro Asp Thr Leu
20 25 30

Asn Gln Gly Glu Phe Lys Glu Leu Val Arg Lys Asp Leu Gln Asn Phe
35 40 45

Leu Lys Lys Glu Asn Lys Asn Glu Lys Val Ile Glu His Ile Met Glu
50 55 60

Asp Leu Asp Thr Asn Ala Asp Lys Gln Leu Ser Phe Glu Glu Phe Ile
65 70 75 80

Met Leu Met Ala Arg Leu Thr Trp Ala Ser His Glu Lys Met His Glu
85 90 95

Gly Asp Glu Gly Pro Gly His His His Lys Pro Gly Leu Gly Glu Gly
100 105 110

Thr Pro

<210> 18
<211> 93
<212> PRT
<213> Homo sapiens

<400> 18
Met Leu Thr Glu Leu Glu Lys Ala Leu Asn Ser Ile Ile Asp Val Tyr
1 5 10 15

His Lys Tyr Ser Leu Ile Lys Gly Asn Phe His Ala Val Tyr Arg Asp
20 25 30

Asp Leu Lys Lys Leu Leu Glu Thr Glu Cys Pro Gln Tyr Ile Arg Lys
 35 40 45

Lys Gly Ala Asp Val Trp Phe Lys Glu Leu Asp Ile Asn Thr Asp Gly
 50 55 60

Ala Val Asn Phe Gln Glu Phe Leu Ile Leu Val Ile Lys Met Gly Val
 65 70 75 80

Ala Ala His Lys Lys Ser His Glu Glu Ser His Lys Glu
 85 90

<210> 19
 <211> 92
 <212> PRT
 <213> Homo sapiens

<400> 19
 Met Thr Lys Leu Glu Glu His Leu Glu Gly Ile Val Asn Ile Phe His
 1 5 10 15

Gln Tyr Ser Val Arg Lys Gly His Phe Asp Thr Leu Ser Lys Gly Glu
 20 25 30

Leu Lys Gln Leu Leu Thr Lys Glu Leu Ala Asn Thr Ile Lys Asn Ile
 35 40 45

Lys Asp Lys Ala Val Ile Asp Glu Ile Phe Gln Gly Leu Asp Ala Asn
 50 55 60

Gln Asp Glu Gln Val Asp Phe Gln Glu Phe Ile Ser Leu Val Ala Ile
 65 70 75 80

Ala Leu Lys Ala Ala His Tyr His Thr His Lys Glu
 85 90

<210> 20
 <211> 92
 <212> PRT
 <213> Homo sapiens

<400> 20
 Met Thr Lys Leu Glu Glu His Leu Glu Gly Ile Val Asn Ile Phe His
 1 5 10 15

Gln Tyr Ser Val Arg Lys Gly His Phe Asp Thr Leu Ser Lys Gly Glu
 20 25 30

Leu Lys Gln Leu Leu Thr Lys Glu Leu Ala Asn Thr Ile Lys Asn Ile
 35 40 45

Lys Asp Lys Ala Val Ile Asp Glu Ile Phe Gln Gly Leu Asp Ala Asn
 50 55 60

Gln Asp Glu Gln Val Asp Phe Gln Glu Phe Ile Ser Leu Val Ala Ile
 65 70 75 80

Ala Leu Lys Ala Ala His Tyr His Thr His Lys Glu

85

90

<210> 21
 <211> 91
 <212> PRT
 <213> Homo sapiens

<400> 21
 Thr Lys Leu Glu Glu His Leu Glu Gly Ile Val Asn Ile Phe His Gln
 1 5 10 15
 Tyr Ser Val Arg Lys Gly His Phe Asp Thr Leu Ser Lys Gly Glu Leu
 20 25 30
 Lys Gln Leu Leu Thr Lys Glu Leu Ala Asn Thr Ile Lys Asn Ile Lys
 35 40 45
 Asp Lys Ala Val Ile Asp Glu Ile Phe Gln Gly Leu Asp Ala Asn Gln
 50 55 60
 Asp Glu Gln Val Asp Phe Gln Glu Phe Ile Ser Leu Val Ala Ile Ala
 65 70 75 80
 Leu Lys Ala Ala His Tyr His Thr His Lys Glu
 85 90

<210> 22
 <211> 93
 <212> PRT
 <213> Homo sapiens

<400> 22
 Met Leu Thr Glu Leu Glu Lys Ala Leu Asn Ser Ile Ile Asp Val Tyr
 1 5 10 15
 His Lys Tyr Ser Leu Ile Lys Gly Asn Phe His Ala Val Tyr Arg Asp
 20 25 30
 Asp Leu Lys Lys Leu Leu Glu Thr Glu Cys Pro Gln Tyr Ile Arg Lys
 35 40 45
 Lys Gly Ala Asp Val Trp Phe Lys Glu Leu Asp Ile Asn Thr Asp Gly
 50 55 60
 Ala Val Asn Phe Gln Glu Phe Leu Ile Leu Val Ile Lys Met Gly Val
 65 70 75 80
 Ala Ala His Lys Lys Ser His Glu Glu Ser His Lys Glu
 85 90

<210> 23
 <211> 92
 <212> PRT
 <213> Homo sapiens

<400> 23
 Met Thr Lys Leu Glu Glu His Leu Glu Gly Ile Val Asn Ile Phe His
 1 5 10 15

65					70						75				80
Lys	Met	Ala	Lys	Glu	Ala	Ile	Phe	Gln	Asp	Thr	Met	Arg	Lys	Phe	Leu
				85					90					95	
Glu	Gln	Glu	Cys	Asn	Val	Leu	Pro	Leu	Lys	Leu	Leu	Met	Pro	Gln	Cys
			100					105					110		
Asn	Gln	Val	Leu	Asp	Asp	Tyr	Phe	Pro	Leu	Val	Ile	Asp	Tyr	Phe	Gln
		115					120					125			
Asn	Gln	Ile	Asp	Ser	Asn	Gly	Ile	Cys	Met	His	Leu	Gly	Leu	Cys	Lys
		130				135					140				
Ser	Arg	Gln	Pro	Glu	Pro	Glu	Gln	Glu	Pro	Gly	Met	Ser	Asp	Pro	Leu
145					150					155					160
Pro	Lys	Pro	Leu	Arg	Asp	Pro	Leu	Pro	Asp	Pro	Leu	Leu	Asp	Lys	Leu
				165					170					175	
Val	Leu	Pro	Val	Leu	Pro	Gly	Ala	Leu	Gln	Ala	Arg	Pro	Gly	Pro	His
			180					185					190		
Thr	Gln	Asp	Leu	Ser	Glu	Gln	Gln	Phe	Pro	Ile	Pro	Leu	Pro	Tyr	Cys
		195					200					205			
Trp	Leu	Cys	Arg	Ala	Leu	Ile	Lys	Arg	Ile	Gln	Ala	Met	Ile	Pro	Lys
	210					215					220				
Gly	Ala	Leu	Arg	Val	Ala	Val	Ala	Gln	Val	Cys	Arg	Val	Val	Pro	Leu
225					230					235					240
Val	Ala	Gly	Gly	Ile	Cys	Gln	Cys	Leu	Ala	Glu	Arg	Tyr	Ser	Val	Ile
				245					250					255	
Leu	Leu	Asp	Thr	Leu	Leu	Gly	Arg	Met	Leu	Pro	Gln	Leu	Val	Cys	Arg
			260					265					270		
Leu	Val	Leu	Arg	Cys	Ser	Met	Asp	Asp	Ser	Ala	Gly	Pro	Arg	Ser	Pro
		275					280					285			
Thr	Gly	Glu	Trp	Leu	Pro	Arg	Asp	Ser	Glu	Cys	His	Leu	Cys	Met	Ser
	290					295					300				
Val	Thr	Thr	Gln	Ala	Gly	Asn	Ser	Ser	Glu	Gln	Ala	Ile	Pro	Gln	Ala
305					310					315					320
Met	Leu	Gln	Ala	Cys	Val	Gly	Ser	Trp	Leu	Asp	Arg	Glu	Lys	Cys	Lys
				325					330					335	
Gln	Phe	Val	Glu	Gln	His	Thr	Pro	Gln	Leu	Leu	Thr	Leu	Val	Pro	Arg
			340					345					350		
Gly	Trp	Asp	Ala	His	Thr	Thr	Cys	Gln	Ala	Leu	Gly	Val	Cys	Gly	Thr
		355					360					365			
Met	Ser	Ser	Pro	Leu	Gln	Cys	Ile	His	Ser	Pro	Asp	Leu			
	370					375					380				

<211> 379

<212> PRT

<213> Homo sapiens

<400> 26

<400> 26
Met Ala Glu Ser His Leu Leu Gln Trp Leu Leu Leu Leu Leu Pro Thr
1 5 10 15

Leu Cys Gly Pro Gly Thr Ala Ala Trp Thr Thr Ser Ser Leu Ala Cys
20 25 30

Ala Gln Gly Pro Glu Phe Trp Cys Gln Ser Leu Glu Gln Ala Leu Gln
35 40 45

Cys Arg Ala Leu Gly His Cys Leu Gln Glu Val Trp Gly His Val Gly
50 55 60

Ala Asp Asp Leu Cys Gln Glu Cys Glu Asp Ile Val His Ile Leu Asn
65 70 75 80

Lys Met Ala Lys Glu Ala Ile Phe Gln Asp Thr Met Arg Lys Phe Leu
85 90 95

Glu Gln Glu Cys Asn Val Leu Pro Leu Lys Leu Leu Met Pro Gln Cys
100 105 110

Asn Gln Val Leu Asp Asp Tyr Phe Pro Leu Val Ile Asp Tyr Phe Gln
115 120 125

Asn Gln Thr Asp Ser Asn Gly Ile Cys Met His Leu Gly Cys Lys Ser
130 135 140

Arg Gln Pro Glu Pro Glu Gln Glu Pro Gly Met Ser Asp Pro Leu Pro
145 150 155 160

Lys Pro Leu Arg Asp Pro Leu Pro Asp Pro Leu Leu Asp Lys Leu Val
165 170 175

Leu Pro Val Leu Pro Gly Ala Leu Gln Ala Arg Pro Gly Pro His Thr
180 185 190

Gln Asp Leu Ser Glu Gln Gln Phe Pro Ile Pro Leu Pro Tyr Cys Trp
195 200 205

Cys Arg Ala Leu Ile Lys Arg Ile Gln Ala Met Ile Pro Lys Gly Ala
210 215 220

Leu Arg Val Ala Val Ala Glñ Val Cys Arg Val Val Pro Leu Val Ala
225 230 235 240

Gly Gly Ile Cys Gln Cys Leu Ala Glu Arg Tyr Ser Val Ile Leu Leu
245 250 255

Asp Thr Leu Leu Gly Arg Met Leu Pro Gln Leu Val Cys Arg Leu Val
260 265 270

Leu Arg Cys Ser Met Asp Asp Ser Ala Gly Pro Arg Ser Pro Thr Gly
275 280 285

Glu Trp Leu Pro Arg Asp Ser Glu Cys His Leu Cys Met Ser Val Thr
290 295 300

Thr Gln Ala Gly Asn Ser Ser Glu Gln Ala Ile Pro Gln Ala Met Leu
305 310 315 320

Gln Ala Cys Val Gly Ser Trp Leu Asp Arg Glu Lys Cys Lys Gln Phe
325 330 335

Val Glu Gln His Thr Pro Gln Leu Leu Thr Leu Val Pro Arg Gly Trp
340 345 350

Asp Ala His Thr Thr Cys Gln Ala Leu Gly Val Cys Gly Thr Met Ser
355 360 365

Ser Pro Leu Gln Cys Ile His Ser Pro Asp Leu
370 375

<210> 27

<211> 527

<212> PRT

<213> Homo sapiens

<400> 27

Met Tyr Ala Leu Phe Leu Leu Ala Ser Leu Leu Gly Ala Ala Leu Ala
1 5 10 15

Gly Pro Val Leu Gly Leu Lys Glu Cys Thr Arg Gly Ser Ala Val Trp
20 25 30

Cys Gln Asn Val Lys Thr Ala Ser Asp Cys Gly Ala Val Lys His Cys
35 40 45

Leu Gln Thr Val Trp Asn Lys Pro Thr Val Lys Ser Leu Pro Cys Asp
50 55 60

Ile Cys Lys Asp Val Val Thr Ala Ala Gly Asp Met Leu Lys Asp Asn
65 70 75 80

Ala Thr Glu Glu Glu Ile Leu Val Tyr Leu Glu Lys Thr Cys Asp Trp
85 90 95

Leu Pro Lys Pro Asn Met Ser Ala Ser Cys Lys Glu Ile Val Asp Ser
100 105 110

Tyr Leu Pro Val Ile Leu Asp Ile Ile Lys Gly Glu Met Ser Arg Pro
115 120 125

Gly Glu Val Cys Ser Ala Leu Asn Leu Cys Glu Ser Leu Gln Lys His
130 135 140

Leu Ala Glu Leu Asn His Gln Lys Gln Leu Glu Ser Asn Lys Ile Pro
145 150 155 160

Glu Leu Asp Met Thr Glu Val Val Ala Pro Phe Met Ala Asn Ile Pro
165 170 175

Leu Leu Leu Tyr Pro Gln Asp Gly Pro Arg Ser Lys Pro Gln Pro Lys
180 185 190

Asp Asn Gly Asp Val Cys Gln Asp Cys Ile Gln Met Val Thr Asp Ile
195 200 205

Gln	Thr	Ala	Val	Arg	Thr	Asn	Ser	Thr	Phe	Val	Gln	Ala	Leu	Val	Glu	210	215	220	
His	Val	Lys	Glu	Glu	Cys	Asp	Arg	Leu	Gly	Pro	Gly	Met	Ala	Asp	Ile	225	230	235	240
Cys	Lys	Asn	Tyr	Ile	Ser	Gln	Tyr	Ser	Glu	Ile	Ala	Ile	Gln	Met	Met	245	250	255	
Met	His	Met	Gln	Asp	Gln	Gln	Pro	Lys	Glu	Ile	Cys	Ala	Leu	Val	Gly	260	265	270	
Phe	Cys	Asp	Glu	Val	Lys	Glu	Met	Pro	Met	Gln	Thr	Leu	Val	Pro	Ala	275	280	285	
Lys	Val	Ala	Ser	Lys	Asn	Val	Ile	Pro	Ala	Leu	Glu	Leu	Val	Glu	Pro	290	295	300	
Ile	Lys	Lys	His	Glu	Val	Pro	Ala	Lys	Ser	Asp	Val	Tyr	Cys	Glu	Val	305	310	315	320
Cys	Glu	Phe	Leu	Val	Lys	Glu	Val	Thr	Lys	Leu	Ile	Asp	Asn	Asn	Lys	325	330	335	
Thr	Glu	Lys	Glu	Ile	Leu	Asp	Ala	Phe	Asp	Lys	Met	Cys	Ser	Lys	Leu	340	345	350	
Pro	Lys	Ser	Leu	Ser	Glu	Glu	Cys	Gln	Glu	Val	Val	Asp	Thr	Tyr	Gly	355	360	365	
Ser	Ser	Ile	Leu	Ser	Ile	Leu	Leu	Glu	Glu	Val	Ser	Pro	Glu	Leu	Val	370	375	380	
Cys	Ser	Met	Leu	His	Leu	Cys	Ser	Gly	Thr	Arg	Leu	Pro	Ala	Leu	Thr	385	390	395	400
Val	His	Val	Thr	Gln	Pro	Lys	Asp	Gly	Gly	Phe	Cys	Glu	Val	Cys	Lys	405	410	415	
Lys	Leu	Val	Gly	Tyr	Leu	Asp	Arg	Asn	Leu	Glu	Lys	Asn	Ser	Thr	Lys	420	425	430	
Gln	Glu	Ile	Leu	Ala	Ala	Leu	Glu	Lys	Gly	Cys	Ser	Phe	Leu	Pro	Asp	435	440	445	
Pro	Tyr	Gln	Lys	Gln	Cys	Asp	Gln	Phe	Val	Ala	Glu	Tyr	Glu	Pro	Val	450	455	460	
Leu	Ile	Glu	Ile	Leu	Val	Glu	Val	Met	Asp	Pro	Ser	Phe	Val	Cys	Leu	465	470	475	480
Lys	Ile	Gly	Ala	Cys	Pro	Ser	Ala	His	Lys	Pro	Leu	Leu	Gly	Thr	Glu	485	490	495	
Lys	Cys	Ile	Trp	Gly	Pro	Ser	Tyr	Trp	Cys	Gln	Asn	Thr	Glu	Thr	Ala	500	505	510	
Ala	Gln	Cys	Asn	Ala	Val	Glu	His	Cys	Lys	Arg	His	Val	Trp	Asn		515	520	525	

<210> 28
 <211> 523
 <212> PRT
 <213> Homo sapiens

<400> 28
 Met Tyr Ala Leu Phe Leu Leu Ala Ser Leu Leu Gly Ala Ala Leu Ala
 1 5 10 15
 Gly Pro Val Leu Gly Leu Lys Glu Cys Thr Arg Gly Ser Ala Val Trp
 20 25 30
 Cys Gln Asn Val Lys Thr Ala Ser Asp Cys Gly Ala Val Lys His Cys
 35 40 45
 Leu Gln Thr Val Trp Asn Lys Pro Thr Val Lys Ser Leu Pro Cys Asp
 50 55 60
 Ile Cys Lys Asp Val Val Thr Ala Ala Gly Asp Met Leu Lys Asp Asn
 65 70 75 80
 Ala Thr Glu Glu Glu Ile Leu Val Tyr Leu Glu Lys Thr Cys Asp Trp
 85 90 95
 Leu Pro Lys Pro Asn Met Ser Ala Ser Cys Lys Glu Ile Val Asp Ser
 100 105 110
 Tyr Leu Pro Val Ile Leu Asp Ile Ile Lys Gly Glu Met Ser Arg Pro
 115 120 125
 Gly Glu Val Cys Ser Ala Leu Leu Cys Glu Ser Leu Gln Lys His Leu
 130 135 140
 Ala Glu Leu Asn His Gln Lys Gln Leu Glu Ser Asn Lys Ile Pro Glu
 145 150 155 160
 Leu Asp Met Thr Glu Val Val Ala Pro Phe Met Ala Asn Ile Pro Leu
 165 170 175
 Leu Leu Tyr Pro Gln Asp Gly Pro Arg Ser Lys Pro Gln Pro Lys Asp
 180 185 190
 Asn Gly Asp Val Cys Gln Asp Cys Ile Gln Met Val Thr Asp Ile Gln
 195 200 205
 Thr Ala Val Arg Thr Asn Ser Thr Phe Val Gln Ala Leu Val Glu His
 210 215 220
 Val Lys Glu Glu Cys Asp Arg Leu Gly Pro Gly Met Ala Asp Ile Cys
 225 230 235 240
 Lys Asn Tyr Ile Ser Gln Tyr Ser Glu Ile Ala Ile Gln Met Met Met
 245 250 255
 His Met Gln Pro Lys Glu Ile Cys Ala Leu Val Gly Phe Cys Asp Glu
 260 265 270
 Val Lys Glu Met Pro Met Gln Thr Leu Val Pro Ala Lys Val Ala Ser
 275 280 285

Lys Asn Val Ile Pro Ala Leu Glu Leu Val Glu Pro Ile Lys Lys His
 290 295 300

Glu Val Pro Ala Lys Ser Asp Val Tyr Cys Glu Val Cys Glu Phe Leu
 305 310 315 320

Val Lys Glu Val Thr Lys Leu Ile Asp Asn Asn Lys Thr Glu Lys Glu
 325 330 335

Ile Leu Asp Ala Phe Asp Lys Met Cys Ser Lys Leu Pro Lys Ser Leu
 340 345 350

Ser Glu Glu Cys Gln Glu Val Val Asp Thr Tyr Gly Ser Ser Ile Leu
 355 360 365

Ser Ile Leu Leu Glu Glu Val Ser Pro Glu Leu Val Cys Ser Met Leu
 370 375 380

His Leu Cys Ser Gly Thr Arg Leu Pro Ala Leu Thr Val His Val Thr
 385 390 395 400

Gln Pro Lys Asp Gly Gly Phe Cys Glu Val Cys Lys Lys Leu Val Gly
 405 410 415

Tyr Leu Asp Arg Asn Leu Glu Lys Asn Ser Thr Lys Gln Glu Ile Leu
 420 425 430

Ala Ala Leu Glu Lys Gly Cys Ser Phe Leu Pro Asp Pro Tyr Gln Lys
 435 440 445

Gln Cys Asp Gln Phe Val Ala Glu Tyr Glu Pro Val Leu Ile Glu Ile
 450 455 460

Leu Val Glu Val Met Asp Pro Ser Phe Val Cys Leu Lys Ile Gly Ala
 465 470 475 480

Cys Pro Ser Ala His Lys Pro Leu Leu Gly Thr Glu Lys Cys Ile Trp
 485 490 495

Gly Pro Ser Tyr Trp Cys Gln Asn Thr Glu Thr Ala Ala Gln Cys Asn
 500 505 510

Ala Val Glu His Cys Lys Arg His Val Trp Asn
 515 520

<210> 29
 <211> 380
 <212> PRT
 <213> Homo sapiens

<400> 29
 Met Ala Glu Ser His Leu Leu Gln Trp Leu Leu Leu Leu Leu Pro Thr
 1 5 10 15

Leu Cys Gly Pro Gly Thr Ala Ala Trp Thr Thr Ser Ser Leu Ala Cys
 20 25 30

Ala Gln Gly Pro Glu Phe Trp Cys Gln Ser Leu Glu Gln Ala Leu Gln
 35 40 45

Cys	Arg	Ala	Leu	Gly	His	Cys	Leu	Gln	Glu	Val	Trp	Gly	His	Val	Gly
50						55					60				
Ala	Asp	Asp	Leu	Cys	Gln	Glu	Cys	Glu	Asp	Ile	Val	His	Ile	Leu	Asn
65					70					75					80
Lys	Met	Ala	Lys	Glu	Ala	Ile	Phe	Gln	Asp	Thr	Met	Arg	Lys	Phe	Leu
				85					90					95	
Glu	Gln	Glu	Cys	Asn	Val	Leu	Pro	Leu	Lys	Leu	Leu	Met	Pro	Gln	Cys
			100					105					110		
Asn	Gln	Val	Leu	Asp	Asp	Tyr	Phe	Pro	Leu	Val	Ile	Asp	Tyr	Phe	Gln
		115					120					125			
Asn	Gln	Thr	Asp	Ser	Asn	Gly	Ile	Cys	Met	His	Gly	Leu	Cys	Lys	Ser
		130				135					140				
Arg	Gln	Pro	Glu	Pro	Glu	Gln	Glu	Pro	Gly	Met	Ser	Asp	Pro	Leu	Pro
145					150					155					160
Lys	Pro	Leu	Arg	Asp	Pro	Leu	Pro	Asp	Pro	Leu	Leu	Asp	Lys	Leu	Val
				165				170						175	
Leu	Pro	Val	Leu	Pro	Gly	Ala	Leu	Gln	Ala	Arg	Pro	Gly	Pro	His	Thr
			180					185					190		
Gln	Asp	Leu	Ser	Glu	Gln	Gln	Phe	Pro	Ile	Pro	Leu	Pro	Tyr	Cys	Trp
		195					200					205			
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<210> 34

<211> 1706

<212> DNA

<213> Homo sapiens

<400> 34

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<212> DNA

<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<210> 37
<211> 1706
<212> DNA
<213> Homo sapiens

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<210> 38
<211> 1043
<212> DNA
<213> Homo sapiens

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<212> DNA
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<211> 1705
<212> DNA

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<213> Homo sapiens

<400> 40

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<211> 1043

<212> DNA

<213> Homo sapiens

<400> 41

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<223> n is a or g or c or t

<220>
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<211> 4195
<212> DNA
<213> Homo sapiens

<400> 43
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<212> DNA

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<211> 406
<212> DNA
<213> Homo sapiens

<400> 45
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<213> Homo sapiens

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<222> 417
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<212> DNA
<213> Homo sapiens

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 <213> Homo sapiens

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 <211> 305
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 <213> Homo sapiens

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Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu
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Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys
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Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro
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Lys	Glu	Glu	Cys	Asp	Arg	Leu	Gly	Pro	Gly	Met	Ala	Asp	Ile	Cys	Lys
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Asn	Tyr	Ile	Ser	Gln	Tyr	Ser	Glu	Ile	Ala	Ile	Gln	Met	Met	Met	His
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Asn	Gln	Gly	Glu	Phe	Lys	Glu	Leu	Val	Arg	Lys	Asp	Leu	Gln	Asn	Phe
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Leu	Lys	Lys	Glu	Asn	Lys	Asn	Glu	Lys	Val	Ile	Glu	His	Ile	Met	Glu
	50					55					60				

Asp	Asp	Leu	Asp	Thr	Asn	Ala	Asp	Lys	Gln	Leu	Ser	Phe	Glu	Glu	Phe
65					70					75					80

Ile	Met	Leu	Met	Ala	Arg	Leu	Thr	Trp	Ala	Ser	His	Glu	Lys	Met	His
				85					90					95	

Glu	Gly	Asp	Glu	Gly	Pro	Gly	His	His	His	Lys	Pro	Gly	Leu	Gly	Glu
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Gly	Thr	Pro
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<141> 2000-07-17

<150> FR9909372

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Thr His Ser Tyr Leu Ser Asp Asp Glu Asp Met Leu Ala Asp Ser Ile
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Glu Ala Val Val Asp Thr Leu Glu Ser Glu Tyr Leu Lys Ile Pro Gly
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Tyr Val Thr Ser Pro Gln Gly Phe Gln Phe Arg Arg Leu Gly Thr Val
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Glu Ala Ala Cys Arg Asn Gly His Cys Ile Pro Arg Asp Tyr Leu Cys
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Asp Gly Gln Glu Asp Cys Glu Asp Gly Ser Asp Glu Leu Asp Cys Gly
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Arg Thr Asp Glu Ala Asn Cys Pro Thr Lys Arg Pro Glu Glu Val Cys
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Tyr Leu Glu His Ser Ala Ala Cys Leu Pro Cys Phe Cys Phe Gly Ile
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Ala Ser Thr His Thr Thr Asn Glu Gly Ile Phe Ser Pro Thr Pro Gly
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Ala Cys Glu Pro Glu Thr Gly Ala Cys Gln Gly Cys Gln His His Thr			
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Gln Arg Gly Thr Pro Gln Asp Cys Gln Leu Cys Pro Cys Tyr Gly Asp			
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1850

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1870

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1880

1885

Cys Ser Ala Thr Gly Ser Pro Thr Pro Thr Leu Glu Trp Thr Gly Gly

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1895

1900

Pro Gly Gly Gln Leu Pro Ala Lys Ala Gln Ile His Gly Gly Ile Leu

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1910

1915

1920

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1925

1930

1935

Ala His Ser Ser Ala Gly Gln Gln Val Ala Arg Ala Val Leu His Val

1940

1945

1950

His Gly Gly Gly Gly Pro Arg Val Gln Val Ser Pro Glu Arg Thr Gln

1955

1960

1965

Val His Ala Gly Arg Thr Val Arg Leu Tyr Cys Arg Ala Ala Gly Val

1970

1975

1980

Pro Ser Ala Thr Ile Thr Trp Arg Lys Glu Gly Gly Ser Leu Pro Pro

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1990

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Gln Ala Arg Ser Glu Arg Thr Asp Ile Ala Thr Leu Leu Ile Pro Ala

2005

2010

2015

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Val Arg His Gln Thr His Gly Ser Leu Leu Arg Leu Tyr Gln Ala Ser			
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Pro Leu Glu Ala Ser Val Leu Val Thr Ile Glu Pro Ala Gly Ser Val			
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Pro Ala Leu Gly Val Thr Pro Thr Val Arg Ile Glu Ser Ser Ser Ser

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2455

2460

Gln Ala His Ala Gln Val Thr Trp His Lys Arg Gly Gly Ser Leu Pro

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2475

2480

Ala Arg His Gln Val His Gly Ser Arg Leu Arg Leu Leu Gln Val Thr

2485

2490

2495

Pro Ala Asp Ser Gly Glu Tyr Val Cys Arg Val Val Gly Ser Ser Gly

2500

2505

2510

Thr Gln Glu Ala Ser Val Leu Val Thr Ile Gln Gln Arg Leu Ser Gly

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2525

Ser His Ser Gln Gly Val Ala Tyr Pro Val Arg Ile Glu Ser Ser Ser

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Ser Gln Ala Pro His Thr Ile Thr Trp Tyr Lys Arg Gly Gly Ser Leu

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2585

2590

Thr Pro Ala Asp Ser Gly Glu Tyr Val Cys His Val Ser Asn Gly Ala

2595

2600

2605

Gly Ser Arg Glu Thr Ser Leu Ile Val Thr Ile Gln Gly Ser Gly Ser

2610

2615

2620

Ser His Val Pro Arg Val Ser Pro Pro Ile Arg Ile Glu Ser Ser Ser

2625 2630 2635 2640

Pro Thr Val Val Glu Gly Gln Thr Leu Asp Leu Asn Cys Val Val Ala

2645 2650 2655

Arg Gln Pro Gln Ala Ile Ile Thr Trp Tyr Lys Arg Gly Gly Ser Leu

2660 2665 2670

Pro Ser Arg His Gln Thr His Gly Ser His Leu Arg Leu His Gln Met

2675 2680 2685

Ser Val Ala Asp Ser Gly Glu Tyr Val Cys Arg Ala Asn Asn Asn Ile

2690 2695 2700

Asp Ala Leu Glu Ala Ser Ile Val Ile Ser Val Ser Pro Ser Ala Gly

2705 2710 2715 2720

Ser Pro Ser Ala Pro Gly Ser Ser Met Pro Ile Arg Ile Glu Ser Ser

2725 2730 2735

Ser Ser His Val Ala Glu Gly Glu Thr Leu Asp Leu Asn Cys Val Val

2740 2745 2750

Pro Gly Gln Ala His Ala Gln Val Thr Trp His Lys Arg Gly Gly Ser

2755 2760 2765

Leu Pro Ser Tyr His Gln Thr Arg Gly Ser Arg Leu Arg Leu His His

2770 2775 2780

Val Ser Pro Ala Asp Ser Gly Glu Tyr Val Cys Arg Val Met Gly Ser

2785 2790 2795 2800

Ser Gly Pro Leu Glu Ala Ser Val Leu Val Thr Ile Glu Ala Ser Gly

2805 2810 2815

Ser Ser Ala Val His Val Pro Ala Pro Gly Gly Ala Pro Pro Ile Arg

2820	2825	2830
Ile Glu Pro Ser Ser Ser Arg Val Ala Glu Gly Gln Thr Leu Asp Leu		
2835	2840	2845
Lys Cys Val Val Pro Gly Gln Ala His Ala Gln Val Thr Trp His Lys		
2850	2855	2860
Arg Gly Gly Asn Leu Pro Ala Arg His Gln Val His Gly Pro Leu Leu		
2865	2870	2875
		2880
Arg Leu Asn Gln Val Ser Pro Ala Asp Ser Gly Glu Tyr Ser Cys Gln		
2885	2890	2895
Val Thr Gly Ser Ser Gly Thr Leu Glu Ala Ser Val Leu Val Thr Ile		
2900	2905	2910
Glu Pro Ser Ser Pro Gly Pro Ile Pro Ala Pro Gly Leu Ala Gln Pro		
2915	2920	2925
Ile Tyr Ile Glu Ala Ser Ser Ser His Val Thr Glu Gly Gln Thr Leu		
2930	2935	2940
Asp Leu Asn Cys Val Val Pro Gly Gln Ala His Ala Gln Val Thr Trp		
2945	2950	2955
		2960
Tyr Lys Arg Gly Gly Ser Leu Pro Ala Arg His Gln Thr His Gly Ser		
2965	2970	2975
Gln Leu Arg Leu His His Val Ser Pro Ala Asp Ser Gly Glu Tyr Val		
2980	2985	2990
Cys Arg Ala Ala Gly Gly Pro Gly Pro Glu Gln Glu Ala Ser Phe Thr		
2995	3000	3005
Val Thr Val Pro Pro Ser Glu Gly Ser Ser Tyr Arg Leu Arg Ser Pro		
3010	3015	3020

Val Ile Ser Ile Asp Pro Pro Ser Ser Thr Val Gln Gln Gly Gln Asp
3025 3030 3035 3040

Ala Ser Phe Lys Cys Leu Ile His Asp Gly Ala Ala Pro Ile Ser Leu
3045 3050 3055

Glu Trp Lys Thr Arg Asn Gln Glu Leu Glu Asp Asn Val His Ile Ser
3060 3065 3070

Pro Asn Gly Ser Ile Ile Thr Ile Val Gly Thr Arg Pro Ser Asn His
3075 3080 3085

Gly Thr Tyr Arg Cys Val Ala Ser Asn Ala Tyr Gly Val Ala Gln Ser
3090 3095 3100

Val Val Asn Leu Ser Val His Gly Pro Pro Thr Val Ser Val Leu Pro
3105 3110 3115 3120

Glu Gly Pro Val Trp Val Lys Val Gly Lys Ala Val Thr Leu Glu Cys
3125 3130 3135

Val Ser Ala Gly Glu Pro Arg Ser Ser Ala Arg Trp Thr Arg Ile Ser
3140 3145 3150

Ser Thr Pro Ala Lys Leu Glu Gln Arg Thr Tyr Gly Leu Met Asp Ser
3155 3160 3165

His Thr Val Leu Gln Ile Ser Ser Ala Lys Pro Ser Asp Ala Gly Thr
3170 3175 3180

Tyr Val Cys Leu Ala Gln Asn Ala Leu Gly Thr Ala Gln Lys Gln Val
3185 3190 3195 3200

Glu Val Ile Val Asp Thr Gly Ala Met Ala Pro Gly Ala Pro Gln Val
3205 3210 3215

Gln Ala Glu Glu Ala Glu Leu Thr Val Glu Ala Gly His Thr Ala Thr

3220

3225

3230

Leu Arg Cys Ser Ala Thr Gly Ser Pro Ala Arg Thr Ile His Trp Ser

3235

3240

3245

Lys Leu Arg Ser Pro Leu Pro Trp Gln His Arg Leu Glu Gly Asp Thr

3250

3255

3260

Leu Ile Ile Pro Arg Val Ala Gln Gln Asp Ser Gly Gln Tyr Ile Cys

3265

3270

3275

3280

Asn Ala Thr Ser Pro Ala Gly His Ala Glu Ala Thr Ile Ile Leu His

3285

3290

3295

Val Glu Ser Pro Pro Tyr Ala Thr Thr Val Pro Glu His Ala Ser Val

3300

3305

3310

Gln Ala Gly Glu Thr Val Gln Leu Gln Cys Leu Ala His Gly Thr Pro

3315

3320

3325

Pro Leu Thr Phe Gln Trp Ser Arg Val Gly Ser Ser Leu Pro Gly Arg

3330

3335

3340

Ala Thr Ala Arg Asn Glu Leu Leu His Phe Glu Arg Ala Ala Pro Glu

3345

3350

3355

3360

Asp Ser Gly Arg Tyr Arg Cys Arg Val Thr Asn Lys Val Gly Ser Ala

3365

3370

3375

Glu Ala Phe Ala Gln Leu Leu Val Gln Gly Pro Pro Gly Ser Leu Pro

3380

3385

3390

Ala Thr Ser Ile Pro Ala Gly Ser Thr Pro Thr Val Gln Val Thr Pro

3395

3400

3405

Gln Leu Glu Thr Lys Ser Ile Gly Ala Ser Val Glu Phe His Cys Ala

3410	3415	3420	
Val Pro Ser Asp Arg Gly Thr Gln Leu Arg Trp Phe Lys Glu Gly Gly			
3425	3430	3435	3440
Gln Leu Pro Pro Gly His Ser Val Gln Asp Gly Val Leu Arg Ile Gln			
	3445	3450	3455
Asn Leu Asp Gln Ser Cys Gln Gly Thr Tyr Ile Cys Gln Ala His Gly			
	3460	3465	3470
Pro Trp Gly Lys Ala Gln Ala Ser Ala Gln Leu Val Ile Gln Ala Leu			
	3475	3480	3485
Pro Ser Val Leu Ile Asn Ile Arg Thr Ser Val Gln Thr Val Val Val			
	3490	3495	3500
Gly His Ala Val Glu Phe Glu Cys Leu Ala Leu Gly Asp Pro Lys Pro			
3505	3510	3515	3520
Gln Val Thr Trp Ser Lys Val Gly Gly His Leu Arg Pro Gly Ile Val			
	3525	3530	3535
Gln Ser Gly Gly Val Val Arg Ile Ala His Val Glu Leu Ala Asp Ala			
	3540	3545	3550
Gly Gln Tyr Arg Cys Thr Ala Thr Asn Ala Ala Gly Thr Thr Gln Ser			
	3555	3560	3565
His Val Leu Leu Leu Val Gln Ala Leu Pro Gln Ile Ser Met Pro Gln			
	3570	3575	3580
Glu Val Arg Val Pro Ala Gly Ser Ala Ala Val Phe Pro Cys Ile Ala			
3585	3590	3595	3600
Ser Gly Tyr Pro Thr Pro Asp Ile Ser Trp Ser Lys Leu Asp Gly Ser			
	3605	3610	3615

Leu Pro Pro Asp Ser Arg Leu Glu Asn Asn Met Leu Met Leu Pro Ser
3620 3625 3630

Val Gln Pro Gln Asp Ala Gly Thr Tyr Val Cys Thr Ala Thr Asn Arg
3635 3640 3645

Gln Gly Lys Val Lys Ala Phe Ala His Leu Gln Val Pro Glu Arg Val
3650 3655 3660

Val Pro Tyr Phe Thr Gln Thr Pro Tyr Ser Phe Leu Pro Leu Pro Thr
3665 3670 3675 3680

Ile Lys Asp Ala Tyr Arg Lys Phe Glu Ile Lys Ile Thr Phe Arg Pro
3685 3690 3695

Asp Ser Ala Asp Gly Met Leu Leu Tyr Asn Gly Gln Lys Arg Val Pro
3700 3705 3710

Gly Ser Pro Thr Asn Leu Ala Asn Arg Gln Pro Asp Phe Ile Ser Phe
3715 3720 3725

Gly Leu Val Gly Gly Arg Pro Glu Phe Arg Phe Asp Ala Gly Ser Gly
3730 3735 3740

Met Ala Thr Ile Arg His Pro Thr Pro Leu Ala Leu Gly His Phe His
3745 3750 3755 3760

Thr Val Thr Leu Leu Arg Ser Leu Thr Gln Gly Ser Leu Ile Val Gly
3765 3770 3775

Asp Leu Ala Pro Val Asn Gly Thr Ser Gln Gly Lys Phe Gln Gly Leu
3780 3785 3790

Asp Leu Asn Glu Glu Leu Tyr Leu Gly Gly Tyr Pro Asp Tyr Gly Ala
3795 3800 3805

Ile Pro Lys Ala Gly Leu Ser Ser Gly Phe Ile Gly Cys Val Arg Glu

3810

3815

3820

Leu Arg Ile Gln Gly Glu Glu Ile Val Phe His Asp Leu Asn Leu Thr

3825

3830

3835

3840

Ala His Gly Ile Ser His Cys Pro Thr Cys Arg Asp Arg Pro Cys Gln

3845

3850

3855

Asn Gly Gly Gln Cys His Asp Ser Glu Ser Ser Ser Tyr Val Cys Val

3860

3865

3870

Cys Pro Ala Gly Phe Thr Gly Ser Arg Cys Glu His Ser Gln Ala Leu

3875

3880

3885

His Cys His Pro Glu Ala Cys Gly Pro Asp Ala Thr Cys Val Asn Arg

3890

3895

3900

Pro Asp Gly Arg Gly Tyr Thr Cys Arg Cys His Leu Gly Arg Ser Gly

3905

3910

3915

3920

Leu Arg Cys Glu Glu Gly Val Thr Val Thr Thr Pro Ser Leu Ser Gly

3925

3930

3935

Ala Gly Ser Tyr Leu Ala Leu Pro Ala Leu Thr Asn Thr His His Glu

3940

3945

3950

Leu Arg Leu Asp Val Glu Phe Lys Pro Leu Ala Pro Asp Gly Val Leu

3955

3960

3965

Leu Phe Ser Gly Gly Lys Ser Gly Pro Val Glu Asp Phe Val Ser Leu

3970

3975

3980

Ala Met Val Gly Gly His Leu Glu Phe Arg Tyr Glu Leu Gly Ser Gly

3985

3990

3995

4000

Leu Ala Val Leu Arg Thr Ala Glu Pro Leu Ala Leu Gly Arg Trp His

4005	4010	4015
Arg Val Ser Ala Glu Arg Leu Asn Lys Asp Gly Ser Leu Arg Val Asn		
4020	4025	4030
Gly Gly Arg Pro Val Leu Arg Ser Ser Pro Gly Lys Ser Gln Gly Leu		
4035	4040	4045
Asn Leu His Thr Leu Leu Tyr Leu Gly Gly Val Glu Pro Ser Val Pro		
4050	4055	4060
Leu Ser Pro Ala Thr Asn Met Ser Ala His Phe Arg Gly Cys Val Gly		
4065	4070	4075
		4080
Glu Val Ser Val Asn Gly Lys Arg Leu Asp Leu Thr Tyr Ser Phe Leu		
4085	4090	4095
Gly Ser Gln Gly Ile Gly Gln Cys Tyr Asp Ser Ser Pro Cys Glu Arg		
4100	4105	4110
Gln Pro Cys Gln His Gly Ala Thr Cys Met Pro Ala Gly Glu Tyr Glu		
4115	4120	4125
Phe Gln Cys Leu Cys Arg Asp Gly Ile Lys Gly Asp Leu Cys Glu His		
4130	4135	4140
Glu Glu Asn Pro Cys Gln Leu Arg Glu Pro Cys Leu His Gly Gly Thr		
4145	4150	4155
		4160
Cys Gln Gly Thr Arg Cys Leu Cys Leu Pro Gly Phe Ser Gly Pro Arg		
4165	4170	4175
Cys Gln Gln Gly Ser Gly His Gly Ile Ala Glu Ser Asp Trp His Leu		
4180	4185	4190
Glu Gly Ser Gly Gly Asn Asp Ala Pro Gly Gln Tyr Gly Ala Tyr Phe		
4195	4200	4205

His Asp Asp Gly Phe Leu Ala Phe Pro Gly His Val Phe Ser Arg Ser

4210

4215

4220

Leu Pro Glu Val Pro Glu Thr Ile Glu Leu Glu Val Arg Thr Ser Thr

4225

4230

4235

4240

Ala Ser Gly Leu Leu Leu Trp Gln Gly Val Glu Val Gly Glu Ala Gly

4245

4250

4255

Gln Gly Lys Asp Phe Ile Ser Leu Gly Leu Gln Asp Gly His Leu Val

4260

4265

4270

Phe Arg Tyr Gln Leu Gly Ser Gly Glu Ala Arg Leu Val Ser Glu Asp

4275

4280

4285

Pro Ile Asn Asp Gly Glu Trp His Arg Val Thr Ala Leu Arg Glu Gly

4290

4295

4300

Arg Arg Gly Ser Ile Gln Val Asp Gly Glu Glu Leu Val Ser Gly Arg

4305

4310

4315

4320

Ser Pro Gly Pro Asn Val Ala Val Asn Ala Lys Gly Ser Ile Tyr Ile

4325

4330

4335

Gly Gly Ala Pro Asp Val Ala Thr Leu Thr Gly Gly Arg Phe Ser Ser

4340

4345

4350

Gly Ile Thr Gly Cys Val Lys Asn Leu Val Leu His Ser Ala Arg Pro

4355

4360

4365

Gly Ala Pro Pro Pro Gln Pro Leu Asp Leu Gln His Arg Ala Gln Ala

4370

4375

4380

Gly Ala Asn Thr Arg Pro Cys Pro Ser

4385

4390

<210> 2

<211> 195

<212> PRT

<213> Homo sapiens

<400> 2

Asp Ala Pro Gly Gln Tyr Gly Ala Tyr Phe His Asp Asp Gly Phe Leu
1 5 10 15

Ala Phe Pro Gly His Val Phe Ser Arg Ser Leu Pro Glu Val Pro Glu
20 25 30

Thr Ile Glu Leu Glu Val Arg Thr Ser Thr Ala Ser Gly Leu Leu Leu
35 40 45

Trp Gln Gly Val Glu Val Gly Glu Ala Gly Gln Gly Lys Asp Phe Ile
50 55 60

Ser Leu Gly Leu Gln Asp Gly His Leu Val Phe Arg Tyr Gln Leu Gly
65 70 75 80

Ser Gly Glu Ala Arg Leu Val Ser Glu Asp Pro Ile Asn Asp Gly Glu
85 90 95

Trp His Arg Val Thr Ala Leu Arg Glu Gly Arg Arg Gly Ser Ile Gln
100 105 110

Val Asp Gly Glu Glu Leu Val Ser Gly Arg Ser Pro Gly Pro Asn Val
115 120 125

Ala Val Asn Ala Lys Gly Ser Val Tyr Ile Gly Gly Ala Pro Asp Val
130 135 140

Ala Thr Leu Thr Gly Gly Arg Phe Ser Ser Gly Ile Thr Gly Cys Val
145 150 155 160

Lys Asn Leu Val Leu His Ser Ala Arg Pro Gly Ala Pro Pro Pro Gln
165 170 175

Pro Leu Asp Leu Gln His Arg Ala Gln Ala Gly Ala Asn Thr Arg Pro
180 185 190

Cys Pro Ser
195

<210> 3
<211> 508
<212> PRT
<213> Homo sapiens

<400> 3
Arg Thr Cys Arg Cys Lys Asn Asn Val Val Gly Arg Leu Cys Asn Glu
1 5 10 15

Cys Ala Asp Arg Ser Phe His Leu Ser Thr Arg Asn Pro Asp Gly Cys
20 25 30

Leu Lys Cys Phe Cys Met Gly Val Ser Arg His Cys Thr Ser Ser Ser
35 40 45

Trp Ser Arg Ala Gln Leu His Gly Ala Ser Glu Glu Pro Gly His Phe
50 55 60

Ser Leu Thr Asn Ala Ala Ser Thr His Thr Thr Asn Glu Gly Ile Phe
65 70 75 80

Ser Pro Thr Pro Gly Glu Leu Gly Phe Ser Ser Phe His Arg Leu Leu
85 90 95

Ser Gly Pro Tyr Phe Trp Ser Leu Pro Ser Arg Phe Leu Gly Asp Lys

100	105	110
Val Thr Ser Tyr Gly Gly Glu Leu Arg Phe Thr Val Thr Gln Arg Ser		
115	120	125
Gln Pro Gly Ser Thr Pro Leu His Gly Gln Pro Leu Val Val Leu Gln		
130	135	140
Gly Asn Asn Ile Ile Leu Glu His His Val Ala Gln Glu Pro Ser Pro		
145	150	155
		160
Gly Gln Pro Ser Thr Phe Ile Val Pro Phe Arg Glu Gln Ala Trp Gln		
165	170	175
Arg Pro Asp Gly Gln Pro Ala Thr Arg Glu His Leu Leu Met Ala Leu		
180	185	190
Ala Gly Ile Asp Thr Leu Leu Ile Arg Ala Ser Tyr Ala Gln Gln Pro		
195	200	205
Ala Glu Ser Arg Leu Ser Gly Ile Ser Met Asp Val Ala Val Pro Glu		
210	215	220
Glu Thr Gly Gln Asp Pro Ala Leu Glu Val Glu Gln Cys Ser Cys Pro		
225	230	235
		240
Pro Gly Tyr Leu Gly Pro Ser Cys Gln Asp Cys Asp Thr Gly Tyr Thr		
245	250	255
Arg Thr Pro Ser Gly Leu Tyr Leu Gly Thr Cys Glu Arg Cys Ser Cys		
260	265	270
His Gly His Ser Glu Ala Cys Glu Pro Glu Thr Gly Ala Cys Gln Gly		
275	280	285
Cys Gln His His Thr Glu Gly Pro Arg Cys Glu Gln Cys Gln Pro Gly		
290	295	300

Tyr Tyr Gly Asp Ala Gln Arg Gly Thr Pro Gln Asp Cys Gln Leu Cys
305 310 315 320

Pro Cys Tyr Gly Asp Pro Ala Ala Gly Gln Ala Ala Leu Thr Cys Phe
325 330 335

Leu Asp Thr Asp Gly His Pro Thr Cys Asp Ala Cys Ser Pro Gly His
340 345 350

Ser Gly Arg His Cys Glu Arg Cys Ala Pro Gly Tyr Tyr Gly Asn Pro
355 360 365

Ser Gln Gly Gln Pro Cys Gln Arg Asp Ser Gln Val Pro Gly Pro Ile
370 375 380

Gly Cys Asn Cys Asp Pro Gln Gly Ser Val Ser Ser Gln Cys Asp Ala
385 390 395 400

Ala Gly Gln Cys Gln Cys Lys Ala Gln Val Glu Gly Leu Thr Cys Ser
405 410 415

His Cys Arg Pro His His Phe His Leu Ser Ala Ser Asn Pro Asp Gly
420 425 430

Cys Leu Pro Cys Phe Cys Met Gly Ile Thr Gln Gln Cys Ala Ser Ser
435 440 445

Ala Tyr Thr Arg His Leu Ile Ser Thr His Phe Ala Pro Gly Asp Phe
450 455 460

Gln Gly Phe Ala Leu Val Asn Pro Gln Arg Asn Ser Arg Leu Thr Gly
465 470 475 480

Glu Phe Thr Val Glu Pro Val Pro Glu Gly Ala Gln Leu Ser Phe Gly
485 490 495

Asn Phe Ala Gln Leu Gly His Glu Ser Phe Tyr Trp
 500 505

<210> 4

<211> 199

<212> PRT

<213> Homo sapiens

<400> 4

Met Lys Trp Val Trp Ala Leu Leu Leu Ala Ala Trp Ala Ala Ala
 1 5 10 15

Glu Arg Asp Cys Arg Val Ser Ser Phe Arg Val Lys Glu Asn Phe Asp
 20 25 30

Lys Ala Arg Phe Ser Gly Thr Trp Tyr Ala Met Ala Lys Lys Asp Pro
 35 40 45

Glu Gly Leu Phe Leu Gln Asp Asn Ile Val Ala Glu Phe Ser Val Asp
 50 55 60

Glu Thr Gly Gln Met Ser Ala Thr Ala Lys Gly Arg Val Arg Leu Leu
 65 70 75 80

Asn Asn Trp Asp Val Cys Ala Asp Met Val Gly Thr Phe Thr Asp Thr
 85 90 95

Glu Asp Pro Ala Lys Phe Lys Met Lys Tyr Trp Gly Val Ala Ser Phe
 100 105 110

Leu Gln Lys Gly Asn Asp Asp His Trp Ile Val Asp Thr Asp Tyr Asp
 115 120 125

Thr Tyr Ala Val Gln Tyr Ser Cys Arg Leu Leu Asn Leu Asp Gly Thr
 130 135 140

Cys Ala Asp Ser Tyr Ser Phe Val Phe Ser Arg Asp Pro Asn Gly Leu
145 150 155 160

Pro Pro Glu Ala Gln Lys Ile Val Arg Gln Arg Gln Glu Glu Leu Cys
165 170 175

Leu Ala Arg Gln Tyr Arg Leu Ile Val His Asn Gly Tyr Cys Asp Gly
180 185 190

Arg Ser Glu Arg Asn Leu Leu
195

<210> 5

<211> 199

<212> PRT

<213> Homo sapiens

<400> 5

Met Lys Trp Val Trp Ala Leu Leu Leu Leu Ala Ala Trp Ala Ala Ala
1 5 10 15

Glu Arg Asp Cys Arg Val Ser Ser Phe Arg Val Lys Glu Asn Phe Asp
20 25 30

Lys Ala Arg Phe Ser Gly Thr Trp Tyr Ala Met Ala Lys Lys Asp Pro
35 40 45

Glu Gly Leu Phe Leu Gln Asp Asn Ile Val Ala Glu Phe Ser Val Asp
50 55 60

Glu Thr Gly Gln Met Ser Ala Thr Ala Lys Gly Arg Val Arg Leu Leu
65 70 75 80

Asn Asn Trp Asp Val Cys Ala Asp Met Val Gly Thr Phe Thr Asp Thr

85 90 95
Glu Asp Pro Ala Lys Phe Lys Met Lys Tyr Trp Gly Val Ala Ser Phe
100 105 110
Leu Gln Lys Gly Asn Asp Asp His Trp Ile Val Asp Thr Asp Tyr Asp
115 120 125
Thr Tyr Ala Val Gln Tyr Ser Cys Arg Leu Leu Asn Leu Asp Gly Thr
130 135 140
Cys Ala Asp Ser Tyr Ser Phe Val Phe Ser Arg Asp Pro Asn Gly Leu
145 150 155 160
Pro Pro Glu Ala Gln Lys Ile Val Arg Gln Arg Gln Glu Glu Leu Cys
165 170 175
Leu Ala Arg Gln Tyr Arg Leu Ile Val His Asn Gly Tyr Cys Asp Gly
180 185 190
Arg Ser Glu Arg Asn Leu Leu
195

<210> 6

<211> 199

<212> PRT

<213> Homo sapiens

<400> 6

Met Lys Trp Val Trp Ala Leu Leu Leu Leu Ala Ala Trp Ala Ala Ala
1 5 10 15
Glu Arg Asp Cys Arg Val Ser Ser Phe Arg Val Lys Glu Asn Phe Asp
20 25 30

Lys Ala Arg Phe Ser Gly Thr Trp Tyr Ala Met Ala Lys Lys Asp Pro

35

40

45

Glu Gly Leu Phe Leu Gln Asp Asn Ile Val Ala Glu Phe Ser Val Asp

50

55

60

Glu Thr Gly Gln Met Ser Ala Thr Ala Lys Gly Arg Val Arg Leu Leu

65

70

75

80

Asn Asn Trp Asp Val Cys Ala Asp Met Val Gly Thr Phe Thr Asp Thr

85

90

95

Glu Asp Pro Ala Lys Phe Lys Met Lys Tyr Trp Gly Val Ala Ser Phe

100

105

110

Leu Gln Lys Gly Asn Asp Asp His Trp Ile Val Asp Thr Asp Tyr Asp

115

120

125

Thr Tyr Ala Val Gln Tyr Ser Cys Arg Leu Leu Asn Leu Asp Gly Thr

130

135

140

Cys Ala Asp Ser Tyr Ser Phe Val Phe Ser Arg Asp Pro Asn Gly Leu

145

150

155

160

Pro Pro Glu Ala Gln Lys Ile Val Arg Gln Arg Gln Glu Glu Leu Cys

165

170

175

Leu Ala Arg Gln Tyr Arg Leu Ile Val His Asn Gly Tyr Cys Asp Gly

180

185

190

Arg Ser Glu Arg Asn Leu Leu

195

<210> 7

<211> 182

<212> PRT

<213> Homo sapiens

<400> 7

Glu Arg Asp Cys Arg Val Ser Ser Phe Arg Val Lys Glu Asn Phe Asp

1 5 10 15

Lys Ala Arg Phe Ser Gly Thr Trp Tyr Ala Met Ala Lys Lys Asp Pro

20 25 30

Glu Gly Leu Phe Leu Gln Asp Asn Ile Val Ala Glu Phe Ser Val Asp

35 40 45

Glu Thr Gly Gln Met Ser Ala Thr Ala Lys Gly Arg Val Arg Leu Leu

50 55 60

Asn Asn Trp Asp Val Cys Ala Asp Met Val Gly Thr Phe Thr Asp Thr

65 70 75 80

Glu Asp Pro Ala Lys Phe Lys Met Lys Tyr Trp Gly Val Ala Ser Phe

85 90 95

Leu Gln Lys Gly Asn Asp Asp His Trp Ile Val Asp Thr Asp Tyr Asp

100 105 110

Thr Tyr Ala Val Gln Tyr Ser Cys Arg Leu Leu Asn Leu Asp Gly Thr

115 120 125

Cys Ala Asp Ser Tyr Ser Phe Val Phe Ser Arg Asp Pro Asn Gly Leu

130 135 140

Pro Pro Glu Ala Gln Lys Ile Val Arg Gln Arg Gln Glu Glu Leu Cys

145 150 155 160

Leu Ala Arg Gln Tyr Arg Leu Ile Val His Asn Gly Tyr Cys Asp Gly

165 170 175

Arg Ser Glu Arg Asn Leu

180

<210> 8

<211> 193

<212> PRT

<213> Homo sapiens

<400> 8

Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu

1

5

10

15

Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser

20

25

30

Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile

35

40

45

Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val

50

55

60

Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu

65

70

75

80

Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys

85

90

95

Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys

100

105

110

Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro

115

120

125

Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr

130

135

140

Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro
145 150 155 160

Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser
165 170 175

Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly
180 185 190

Ile

<210> 9

<211> 193

<212> PRT

<213> Homo sapiens

<400> 9

Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu
1 5 10 15

Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser
20 25 30

Ser Phe Ser Trp Asp Asn Cys Phe Glu Gly Lys Asp Pro Ala Val Ile
35 40 45

Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val
50 55 60

Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu
65 70 75 80

Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys

85 90 95
Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys
100 105 110
Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro
115 120 125
Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr
130 135 140
Tyr Ser Leu Pro Lys Ser Glu Phe Ala Val Pro Asp Leu Glu Leu Pro
145 150 155 160
Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser
165 170 175
Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly
180 185 190
Ile

<210> 10

<211> 178

<212> PRT

<213> Homo sapiens

<400> 10

Leu Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu
1 5 10 15

Ser Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val
20 25 30

[illegible]

Ile Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn

35

40

45

Val Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro

50

55

60

Leu Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile

65

70

75

80

Lys Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe

85

90

95

Cys Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu

100

105

110

Pro Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly

115

120

125

Thr Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu

130

135

140

Pro Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser

145

150

155

160

Ser Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys

165

170

175

Gly Ile

<210> 11

<211> 200

<212> PRT

<213> Homo sapiens

<400> 11

Arg Ala Gly Pro Pro Phe Pro Met Gln Ser Leu Met Gln Ala Pro Leu

1 5 10 15

Leu Ile Ala Leu Gly Leu Leu Leu Ala Ala Pro Ala Gln Ala His Leu

20 25 30

Lys Lys Pro Ser Gln Leu Ser Ser Phe Ser Trp Asp Asn Cys Asp Glu

35 40 45

Gly Lys Asp Pro Ala Val Ile Arg Ser Leu Thr Leu Glu Pro Asp Pro

50 55 60

Ile Ile Val Pro Gly Asn Val Thr Leu Ser Val Met Gly Ser Thr Ser

65 70 75 80

Val Pro Leu Ser Ser Pro Leu Lys Val Asp Leu Val Leu Glu Lys Glu

85 90 95

Val Ala Gly Leu Trp Ile Lys Ile Pro Cys Thr Asp Tyr Ile Gly Ser

100 105 110

Cys Thr Phe Glu His Phe Cys Asp Val Leu Asp Met Leu Ile Pro Thr

115 120 125

Gly Glu Pro Cys Pro Glu Pro Leu Arg Thr Tyr Gly Leu Pro Cys His

130 135 140

Cys Pro Phe Lys Glu Gly Thr Tyr Ser Leu Pro Lys Ser Glu Phe Val

145 150 155 160

Val Pro Asp Leu Glu Leu Pro Ser Trp Leu Thr Thr Gly Asn Tyr Arg

165 170 175

Ile Glu Ser Val Leu Ser Ser Ser Gly Lys Arg Leu Gly Cys Ile Lys

180 185 190

Ile Ala Ala Ser Leu Lys Gly Ile

195

200

<210> 12

<211> 189

<212> PRT

<213> Homo sapiens

<400> 12

Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu Leu Ala Thr Pro

1

5

10

15

Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser Ser Phe Ser Trp

20

25

30

Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile Arg Ser Leu Thr

35

40

45

Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val Thr Leu Ser Val

50

55

60

Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu Lys Val Asp Leu

65

70

75

80

Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys Ile Pro Cys Thr

85

90

95

Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys Asp Val Leu Asp

100

105

110

Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro Leu Arg Thr Tyr

115

120

125

Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr Tyr Ser Leu Pro

130

135

140

Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro Ser Trp Leu Thr
145 150 155 160

Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser Ser Gly Lys Arg
165 170 175

Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly Ile
180 185

<210> 13

<211> 193

<212> PRT

<213> Homo sapiens

<400> 13

Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu
1 5 10 15

Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser
20 25 30

Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile
35 40 45

Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val
50 55 60

Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu
65 70 75 80

Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys
85 90 95

Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys

	100	105	110
Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro			
	115	120	125
Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr			
	130	135	140
Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro			
145	150	155	160
Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser			
	165	170	175
Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly			
	180	185	190
Ile			

<210> 14
 <211> 193
 <212> PRT
 <213> Homo sapiens

<400> 14
 Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu
 1 5 10 15
 Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser
 20 25 30
 Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile
 35 40 45

Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val

50

55

60

Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu

65

70

75

80

Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys

85

90

95

Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys

100

105

110

Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro

115

120

125

Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr

130

135

140

Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro

145

150

155

160

Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser

165

170

175

Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly

180

185

190

Ile

<210> 15

<211> 193

<212> PRT

<213> Homo sapiens

<400> 15

Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu

1 5 10 15

Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser

20 25 30

Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile

35 40 45

Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val

50 55 60

Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu

65 70 75 80

Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys

85 90 95

Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys

100 105 110

Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro

115 120 125

Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr

130 135 140

Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro

145 150 155 160

Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser

165 170 175

Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly

180 185 190

Ile

<210> 16

<211> 193

<212> PRT

<213> Homo sapiens

<400> 16

Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu
1 5 10 15

Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser
20 25 30

Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile
35 40 45

Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val
50 55 60

Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu
65 70 75 80

Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys
85 90 95

Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys
100 105 110

Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro
115 120 125

Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr
130 135 140

Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro
145 150 155 160

Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser
165 170 175

Ser Gly Lys Arg Leu Gly Cys Ile Lys Ile Ala Ala Ser Leu Lys Gly
180 185 190

Ile

<210> 17

<211> 114

<212> PRT

<213> Homo sapiens

<400> 17

Met Thr Cys Lys Met Ser Gln Leu Glu Arg Asn Ile Glu Thr Ile Ile
1 5 10 15

Asn Thr Phe His Gln Tyr Ser Val Lys Leu Gly His Pro Asp Thr Leu
20 25 30

Asn Gln Gly Glu Phe Lys Glu Leu Val Arg Lys Asp Leu Gln Asn Phe
35 40 45

Leu Lys Lys Glu Asn Lys Asn Glu Lys Val Ile Glu His Ile Met Glu
50 55 60

Asp Leu Asp Thr Asn Ala Asp Lys Gln Leu Ser Phe Glu Glu Phe Ile
65 70 75 80

Met Leu Met Ala Arg Leu Thr Trp Ala Ser His Glu Lys Met His Glu

85 90 95
Gly Asp Glu Gly Pro Gly His His His Lys Pro Gly Leu Gly Glu Gly
100 105 110

Thr Pro

<210> 18
<211> 93
<212> PRT
<213> Homo sapiens

<400> 18
Met Leu Thr Glu Leu Glu Lys Ala Leu Asn Ser Ile Ile Asp Val Tyr
1 5 10 15

His Lys Tyr Ser Leu Ile Lys Gly Asn Phe His Ala Val Tyr Arg Asp
20 25 30

Asp Leu Lys Lys Leu Leu Glu Thr Glu Cys Pro Gln Tyr Ile Arg Lys
35 40 45

Lys Gly Ala Asp Val Trp Phe Lys Glu Leu Asp Ile Asn Thr Asp Gly
50 55 60

Ala Val Asn Phe Gln Glu Phe Leu Ile Leu Val Ile Lys Met Gly Val
65 70 75 80

Ala Ala His Lys Lys Ser His Glu Glu Ser His Lys Glu
85 90

<210> 19

<211> 92

<212> PRT

<213> Homo sapiens

<400> 19

Met Thr Lys Leu Glu Glu His Leu Glu Gly Ile Val Asn Ile Phe His
1 5 10 15

Gln Tyr Ser Val Arg Lys Gly His Phe Asp Thr Leu Ser Lys Gly Glu
20 25 30

Leu Lys Gln Leu Leu Thr Lys Glu Leu Ala Asn Thr Ile Lys Asn Ile
35 40 45

Lys Asp Lys Ala Val Ile Asp Glu Ile Phe Gln Gly Leu Asp Ala Asn
50 55 60

Gln Asp Glu Gln Val Asp Phe Gln Glu Phe Ile Ser Leu Val Ala Ile
65 70 75 80

Ala Leu Lys Ala Ala His Tyr His Thr His Lys Glu
85 90

<210> 20

<211> 92

<212> PRT

<213> Homo sapiens

<400> 20

Met Thr Lys Leu Glu Glu His Leu Glu Gly Ile Val Asn Ile Phe His
1 5 10 15

Gln Tyr Ser Val Arg Lys Gly His Phe Asp Thr Leu Ser Lys Gly Glu
20 25 30

Leu Lys Gln Leu Leu Thr Lys Glu Leu Ala Asn Thr Ile Lys Asn Ile
 35 40 45

Lys Asp Lys Ala Val Ile Asp Glu Ile Phe Gln Gly Leu Asp Ala Asn
 50 55 60

Gln Asp Glu Gln Val Asp Phe Gln Glu Phe Ile Ser Leu Val Ala Ile
 65 70 75 80

Ala Leu Lys Ala Ala His Tyr His Thr His Lys Glu
 85 90

<210> 21

<211> 91

<212> PRT

<213> Homo sapiens

<400> 21

Thr Lys Leu Glu Glu His Leu Glu Gly Ile Val Asn Ile Phe His Gln
 1 5 10 15

Tyr Ser Val Arg Lys Gly His Phe Asp Thr Leu Ser Lys Gly Glu Leu
 20 25 30

Lys Gln Leu Leu Thr Lys Glu Leu Ala Asn Thr Ile Lys Asn Ile Lys
 35 40 45

Asp Lys Ala Val Ile Asp Glu Ile Phe Gln Gly Leu Asp Ala Asn Gln
 50 55 60

Asp Glu Gln Val Asp Phe Gln Glu Phe Ile Ser Leu Val Ala Ile Ala
 65 70 75 80

Leu Lys Ala Ala His Tyr His Thr His Lys Glu
 85 90

<210> 22

<211> 93

<212> PRT

<213> Homo sapiens

<400> 22

Met Leu Thr Glu Leu Glu Lys Ala Leu Asn Ser Ile Ile Asp Val Tyr
1 5 10 15

His Lys Tyr Ser Leu Ile Lys Gly Asn Phe His Ala Val Tyr Arg Asp
20 25 30

Asp Leu Lys Lys Leu Leu Glu Thr Glu Cys Pro Gln Tyr Ile Arg Lys
35 40 45

Lys Gly Ala Asp Val Trp Phe Lys Glu Leu Asp Ile Asn Thr Asp Gly
50 55 60

Ala Val Asn Phe Gln Glu Phe Leu Ile Leu Val Ile Lys Met Gly Val
65 70 75 80

Ala Ala His Lys Lys Ser His Glu Glu Ser His Lys Glu
85 90

<210> 23

<211> 92

<212> PRT

<213> Homo sapiens

<400> 23

Met Thr Lys Leu Glu Glu His Leu Glu Gly Ile Val Asn Ile Phe His
1 5 10 15

Gln Tyr Ser Val Arg Lys Gly His Phe Asp Thr Leu Ser Lys Gly Glu

20

25

30

Leu Lys Gln Leu Leu Thr Lys Glu Leu Ala Asn Thr Ile Lys Asn Ile

35

40

45

Lys Asp Lys Ala Val Ile Asp Glu Ile Phe Gln Gly Leu Asp Ala Asn

50

55

60

Gln Asp Glu Gln Val Asp Phe Gln Glu Phe Ile Ser Leu Val Ala Ile

65

70

75

80

Ala Leu Lys Ala Ala His Tyr His Thr His Lys Glu

85

90

<210> 24

<211> 85

<212> PRT

<213> Homo sapiens

<400> 24

Asp Asn Gly Asp Val Cys Gln Asp Cys Ile Gln Met Val Thr Asp Ile

1

5

10

15

Gln Thr Ala Val Arg Thr Asn Ser Thr Phe Val Gln Ala Leu Val Glu

20

25

30

His Val Lys Glu Glu Cys Asp Arg Leu Gly Pro Gly Met Ala Asp Ile

35

40

45

Cys Lys Asn Tyr Ile Ser Gln Tyr Ser Glu Ile Ala Ile Gln Met Met

50

55

60

Met His Met Gln Asp Gln Gln Pro Lys Glu Ile Cys Ala Leu Val Gly

65 70 75 80

Phe Cys Asp Glu Val

85

<210> 25

<211> 381

<212> PRT

<213> Homo sapiens

<400> 25

Met Ala Glu Ser His Leu Leu Gln Trp Leu Leu Leu Leu Pro Thr

1 5 10 15

Leu Cys Gly Pro Gly Thr Ala Ala Trp Thr Thr Ser Ser Leu Ala Cys

20 25 30

Ala Gln Gly Pro Glu Phe Trp Cys Gln Ser Leu Glu Gln Ala Leu Gln

35 40 45

Cys Arg Ala Leu Gly His Cys Leu Gln Glu Val Trp Gly His Val Gly

50 55 60

Ala Asp Asp Leu Cys Gln Glu Cys Glu Asp Ile Val His Ile Leu Asn

65 70 75 80

Lys Met Ala Lys Glu Ala Ile Phe Gln Asp Thr Met Arg Lys Phe Leu

85 90 95

Glu Gln Glu Cys Asn Val Leu Pro Leu Lys Leu Leu Met Pro Gln Cys

100 105 110

Asn Gln Val Leu Asp Asp Tyr Phe Pro Leu Val Ile Asp Tyr Phe Gln

115 120 125

Asn Gln Ile Asp Ser Asn Gly Ile Cys Met His Leu Gly Leu Cys Lys

130

135

140

Ser Arg Gln Pro Glu Pro Glu Gln Glu Pro Gly Met Ser Asp Pro Leu

145

150

155

160

Pro Lys Pro Leu Arg Asp Pro Leu Pro Asp Pro Leu Leu Asp Lys Leu

165

170

175

Val Leu Pro Val Leu Pro Gly Ala Leu Gln Ala Arg Pro Gly Pro His

180

185

190

Thr Gln Asp Leu Ser Glu Gln Gln Phe Pro Ile Pro Leu Pro Tyr Cys

195

200

205

Trp Leu Cys Arg Ala Leu Ile Lys Arg Ile Gln Ala Met Ile Pro Lys

210

215

220

Gly Ala Leu Arg Val Ala Val Ala Gln Val Cys Arg Val Val Pro Leu

225

230

235

240

Val Ala Gly Gly Ile Cys Gln Cys Leu Ala Glu Arg Tyr Ser Val Ile

245

250

255

Leu Leu Asp Thr Leu Leu Gly Arg Met Leu Pro Gln Leu Val Cys Arg

260

265

270

Leu Val Leu Arg Cys Ser Met Asp Asp Ser Ala Gly Pro Arg Ser Pro

275

280

285

Thr Gly Glu Trp Leu Pro Arg Asp Ser Glu Cys His Leu Cys Met Ser

290

295

300

Val Thr Thr Gln Ala Gly Asn Ser Ser Glu Gln Ala Ile Pro Gln Ala

305

310

315

320

Met Leu Gln Ala Cys Val Gly Ser Trp Leu Asp Arg Glu Lys Cys Lys

325 330 335
 Gln Phe Val Glu Gln His Thr Pro Gln Leu Leu Thr Leu Val Pro Arg
 340 345 350
 Gly Trp Asp Ala His Thr Thr Cys Gln Ala Leu Gly Val Cys Gly Thr
 355 360 365
 Met Ser Ser Pro Leu Gln Cys Ile His Ser Pro Asp Leu
 370 375 380

<210> 26

<211> 379

<212> PRT

<213> Homo sapiens

<400> 26

Met Ala Glu Ser His Leu Leu Gln Trp Leu Leu Leu Leu Leu Pro Thr
 1 5 10 15

Leu Cys Gly Pro Gly Thr Ala Ala Trp Thr Thr Ser Ser Leu Ala Cys
 20 25 30

Ala Gln Gly Pro Glu Phe Trp Cys Gln Ser Leu Glu Gln Ala Leu Gln
 35 40 45

Cys Arg Ala Leu Gly His Cys Leu Gln Glu Val Trp Gly His Val Gly
 50 55 60

Ala Asp Asp Leu Cys Gln Glu Cys Glu Asp Ile Val His Ile Leu Asn
 65 70 75 80

Lys Met Ala Lys Glu Ala Ile Phe Gln Asp Thr Met Arg Lys Phe Leu
 85 90 95

Glu Gln Glu Cys Asn Val Leu Pro Leu Lys Leu Leu Met Pro Gln Cys
 100 105 110

Asn Gln Val Leu Asp Asp Tyr Phe Pro Leu Val Ile Asp Tyr Phe Gln
 115 120 125

Asn Gln Thr Asp Ser Asn Gly Ile Cys Met His Leu Gly Cys Lys Ser
 130 135 140

Arg Gln Pro Glu Pro Glu Gln Glu Pro Gly Met Ser Asp Pro Leu Pro
 145 150 155 160

Lys Pro Leu Arg Asp Pro Leu Pro Asp Pro Leu Leu Asp Lys Leu Val
 165 170 175

Leu Pro Val Leu Pro Gly Ala Leu Gln Ala Arg Pro Gly Pro His Thr
 180 185 190

Gln Asp Leu Ser Glu Gln Gln Phe Pro Ile Pro Leu Pro Tyr Cys Trp
 195 200 205

Cys Arg Ala Leu Ile Lys Arg Ile Gln Ala Met Ile Pro Lys Gly Ala
 210 215 220

Leu Arg Val Ala Val Ala Gln Val Cys Arg Val Val Pro Leu Val Ala
 225 230 235 240

Gly Gly Ile Cys Gln Cys Leu Ala Glu Arg Tyr Ser Val Ile Leu Leu
 245 250 255

Asp Thr Leu Leu Gly Arg Met Leu Pro Gln Leu Val Cys Arg Leu Val
 260 265 270

Leu Arg Cys Ser Met Asp Asp Ser Ala Gly Pro Arg Ser Pro Thr Gly
 275 280 285

Glu Trp Leu Pro Arg Asp Ser Glu Cys His Leu Cys Met Ser Val Thr

290 295 300
Thr Gln Ala Gly Asn Ser Ser Glu Gln Ala Ile Pro Gln Ala Met Leu
305 310 315 320
Gln Ala Cys Val Gly Ser Trp Leu Asp Arg Glu Lys Cys Lys Gln Phe
325 330 335
Val Glu Gln His Thr Pro Gln Leu Leu Thr Leu Val Pro Arg Gly Trp
340 345 350
Asp Ala His Thr Thr Cys Gln Ala Leu Gly Val Cys Gly Thr Met Ser
355 360 365
Ser Pro Leu Gln Cys Ile His Ser Pro Asp Leu
370 375

<210> 27

<211> 527

<212> PRT

<213> Homo sapiens

<400> 27

Met Tyr Ala Leu Phe Leu Leu Ala Ser Leu Leu Gly Ala Ala Leu Ala
1 5 10 15

Gly Pro Val Leu Gly Leu Lys Glu Cys Thr Arg Gly Ser Ala Val Trp
20 25 30

Cys Gln Asn Val Lys Thr Ala Ser Asp Cys Gly Ala Val Lys His Cys
35 40 45

Leu Gln Thr Val Trp Asn Lys Pro Thr Val Lys Ser Leu Pro Cys Asp
50 55 60

Ile Cys Lys Asp Val Val Thr Ala Ala Gly Asp Met Leu Lys Asp Asn

65 70 75 80

Ala Thr Glu Glu Glu Ile Leu Val Tyr Leu Glu Lys Thr Cys Asp Trp

85 90 95

Leu Pro Lys Pro Asn Met Ser Ala Ser Cys Lys Glu Ile Val Asp Ser

100 105 110

Tyr Leu Pro Val Ile Leu Asp Ile Ile Lys Gly Glu Met Ser Arg Pro

115 120 125

Gly Glu Val Cys Ser Ala Leu Asn Leu Cys Glu Ser Leu Gln Lys His

130 135 140

Leu Ala Glu Leu Asn His Gln Lys Gln Leu Glu Ser Asn Lys Ile Pro

145 150 155 160

Glu Leu Asp Met Thr Glu Val Val Ala Pro Phe Met Ala Asn Ile Pro

165 170 175

Leu Leu Leu Tyr Pro Gln Asp Gly Pro Arg Ser Lys Pro Gln Pro Lys

180 185 190

Asp Asn Gly Asp Val Cys Gln Asp Cys Ile Gln Met Val Thr Asp Ile

195 200 205

Gln Thr Ala Val Arg Thr Asn Ser Thr Phe Val Gln Ala Leu Val Glu

210 215 220

His Val Lys Glu Glu Cys Asp Arg Leu Gly Pro Gly Met Ala Asp Ile

225 230 235 240

Cys Lys Asn Tyr Ile Ser Gln Tyr Ser Glu Ile Ala Ile Gln Met Met

245 250 255

Met His Met Gln Asp Gln Gln Pro Lys Glu Ile Cys Ala Leu Val Gly

260	265	270
Phe Cys Asp Glu Val Lys Glu Met Pro Met Gln Thr Leu Val Pro Ala		
275	280	285
Lys Val Ala Ser Lys Asn Val Ile Pro Ala Leu Glu Leu Val Glu Pro		
290	295	300
Ile Lys Lys His Glu Val Pro Ala Lys Ser Asp Val Tyr Cys Glu Val		
305	310	315
		320
Cys Glu Phe Leu Val Lys Glu Val Thr Lys Leu Ile Asp Asn Asn Lys		
325	330	335
Thr Glu Lys Glu Ile Leu Asp Ala Phe Asp Lys Met Cys Ser Lys Leu		
340	345	350
Pro Lys Ser Leu Ser Glu Glu Cys Gln Glu Val Val Asp Thr Tyr Gly		
355	360	365
Ser Ser Ile Leu Ser Ile Leu Leu Glu Glu Val Ser Pro Glu Leu Val		
370	375	380
Cys Ser Met Leu His Leu Cys Ser Gly Thr Arg Leu Pro Ala Leu Thr		
385	390	395
		400
Val His Val Thr Gln Pro Lys Asp Gly Gly Phe Cys Glu Val Cys Lys		
405	410	415
Lys Leu Val Gly Tyr Leu Asp Arg Asn Leu Glu Lys Asn Ser Thr Lys		
420	425	430
Gln Glu Ile Leu Ala Ala Leu Glu Lys Gly Cys Ser Phe Leu Pro Asp		
435	440	445
Pro Tyr Gln Lys Gln Cys Asp Gln Phe Val Ala Glu Tyr Glu Pro Val		
450	455	460

Leu Ile Glu Ile Leu Val Glu Val Met Asp Pro Ser Phe Val Cys Leu
465 470 475 480

Lys Ile Gly Ala Cys Pro Ser Ala His Lys Pro Leu Leu Gly Thr Glu
485 490 495

Lys Cys Ile Trp Gly Pro Ser Tyr Trp Cys Gln Asn Thr Glu Thr Ala
500 505 510

Ala Gln Cys Asn Ala Val Glu His Cys Lys Arg His Val Trp Asn
515 520 525

<210> 28

<211> 523

<212> PRT

<213> Homo sapiens

<400> 28

Met Tyr Ala Leu Phe Leu Leu Ala Ser Leu Leu Gly Ala Ala Leu Ala
1 5 10 15

Gly Pro Val Leu Gly Leu Lys Glu Cys Thr Arg Gly Ser Ala Val Trp
20 25 30

Cys Gln Asn Val Lys Thr Ala Ser Asp Cys Gly Ala Val Lys His Cys
35 40 45

Leu Gln Thr Val Trp Asn Lys Pro Thr Val Lys Ser Leu Pro Cys Asp
50 55 60

Ile Cys Lys Asp Val Val Thr Ala Ala Gly Asp Met Leu Lys Asp Asn
65 70 75 80

Ala Thr Glu Glu Glu Ile Leu Val Tyr Leu Glu Lys Thr Cys Asp Trp

	85	90	95
Leu Pro Lys Pro Asn Met Ser Ala Ser Cys Lys Glu Ile Val Asp Ser			
	100	105	110
Tyr Leu Pro Val Ile Leu Asp Ile Ile Lys Gly Glu Met Ser Arg Pro			
	115	120	125
Gly Glu Val Cys Ser Ala Leu Leu Cys Glu Ser Leu Gln Lys His Leu			
	130	135	140
Ala Glu Leu Asn His Gln Lys Gln Leu Glu Ser Asn Lys Ile Pro Glu			
145	150	155	160
Leu Asp Met Thr Glu Val Val Ala Pro Phe Met Ala Asn Ile Pro Leu			
	165	170	175
Leu Leu Tyr Pro Gln Asp Gly Pro Arg Ser Lys Pro Gln Pro Lys Asp			
	180	185	190
Asn Gly Asp Val Cys Gln Asp Cys Ile Gln Met Val Thr Asp Ile Gln			
	195	200	205
Thr Ala Val Arg Thr Asn Ser Thr Phe Val Gln Ala Leu Val Glu His			
	210	215	220
Val Lys Glu Glu Cys Asp Arg Leu Gly Pro Gly Met Ala Asp Ile Cys			
225	230	235	240
Lys Asn Tyr Ile Ser Gln Tyr Ser Glu Ile Ala Ile Gln Met Met Met			
	245	250	255
His Met Gln Pro Lys Glu Ile Cys Ala Leu Val Gly Phe Cys Asp Glu			
	260	265	270
Val Lys Glu Met Pro Met Gln Thr Leu Val Pro Ala Lys Val Ala Ser			
	275	280	285

Lys Asn Val Ile Pro Ala Leu Glu Leu Val Glu Pro Ile Lys Lys His

290

295

300

Glu Val Pro Ala Lys Ser Asp Val Tyr Cys Glu Val Cys Glu Phe Leu

305

310

315

320

Val Lys Glu Val Thr Lys Leu Ile Asp Asn Asn Lys Thr Glu Lys Glu

325

330

335

Ile Leu Asp Ala Phe Asp Lys Met Cys Ser Lys Leu Pro Lys Ser Leu

340

345

350

Ser Glu Glu Cys Gln Glu Val Val Asp Thr Tyr Gly Ser Ser Ile Leu

355

360

365

Ser Ile Leu Leu Glu Glu Val Ser Pro Glu Leu Val Cys Ser Met Leu

370

375

380

His Leu Cys Ser Gly Thr Arg Leu Pro Ala Leu Thr Val His Val Thr

385

390

395

400

Gln Pro Lys Asp Gly Gly Phe Cys Glu Val Cys Lys Lys Leu Val Gly

405

410

415

Tyr Leu Asp Arg Asn Leu Glu Lys Asn Ser Thr Lys Gln Glu Ile Leu

420

425

430

Ala Ala Leu Glu Lys Gly Cys Ser Phe Leu Pro Asp Pro Tyr Gln Lys

435

440

445

Gln Cys Asp Gln Phe Val Ala Glu Tyr Glu Pro Val Leu Ile Glu Ile

450

455

460

Leu Val Glu Val Met Asp Pro Ser Phe Val Cys Leu Lys Ile Gly Ala

465

470

475

480

Cys Pro Ser Ala His Lys Pro Leu Leu Gly Thr Glu Lys Cys Ile Trp
485 490 495

Gly Pro Ser Tyr Trp Cys Gln Asn Thr Glu Thr Ala Ala Gln Cys Asn
500 505 510

Ala Val Glu His Cys Lys Arg His Val Trp Asn
515 520

<210> 29

<211> 380

<212> PRT

<213> Homo sapiens

<400> 29

Met Ala Glu Ser His Leu Leu Gln Trp Leu Leu Leu Leu Leu Pro Thr
1 5 10 15

Leu Cys Gly Pro Gly Thr Ala Ala Trp Thr Thr Ser Ser Leu Ala Cys
20 25 30

Ala Gln Gly Pro Glu Phe Trp Cys Gln Ser Leu Glu Gln Ala Leu Gln
35 40 45

Cys Arg Ala Leu Gly His Cys Leu Gln Glu Val Trp Gly His Val Gly
50 55 60

Ala Asp Asp Leu Cys Gln Glu Cys Glu Asp Ile Val His Ile Leu Asn
65 70 75 80

Lys Met Ala Lys Glu Ala Ile Phe Gln Asp Thr Met Arg Lys Phe Leu
85 90 95

Glu Gln Glu Cys Asn Val Leu Pro Leu Lys Leu Leu Met Pro Gln Cys
100 105 110

Asn Gln Val Leu Asp Asp Tyr Phe Pro Leu Val Ile Asp Tyr Phe Gln

115

120

125

Asn Gln Thr Asp Ser Asn Gly Ile Cys Met His Gly Leu Cys Lys Ser

130

135

140

Arg Gln Pro Glu Pro Glu Gln Glu Pro Gly Met Ser Asp Pro Leu Pro

145

150

155

160

Lys Pro Leu Arg Asp Pro Leu Pro Asp Pro Leu Leu Asp Lys Leu Val

165

170

175

Leu Pro Val Leu Pro Gly Ala Leu Gln Ala Arg Pro Gly Pro His Thr

180

185

190

Gln Asp Leu Ser Glu Gln Gln Phe Pro Ile Pro Leu Pro Tyr Cys Trp

195

200

205

Leu Cys Arg Ala Leu Ile Lys Arg Ile Gln Ala Met Ile Pro Lys Gly

210

215

220

Ala Leu Ala Val Ala Val Ala Gln Val Cys Arg Val Val Pro Leu Val

225

230

235

240

Ala Gly Gly Ile Cys Gln Cys Leu Ala Glu Arg Tyr Ser Val Ile Leu

245

250

255

Leu Asp Thr Leu Leu Gly Arg Met Leu Pro Gln Leu Val Cys Arg Leu

260

265

270

Val Leu Arg Cys Ser Met Asp Asp Ser Ala Gly Pro Arg Ser Pro Thr

275

280

285

Gly Glu Trp Leu Pro Arg Asp Ser Glu Cys His Leu Cys Met Ser Val

290

295

300

Thr Thr Gln Ala Gly Asn Ser Ser Glu Gln Ala Ile Pro Gln Ala Met

305 310 315 320

Leu Gln Ala Cys Val Gly Ser Trp Leu Asp Arg Glu Lys Cys Lys Gln

325 330 335

Phe Val Glu Gln His Thr Pro Gln Leu Leu Thr Leu Val Pro Arg Gly

340 345 350

Trp Asp Ala His Thr Thr Cys Gln Ala Leu Gly Val Cys Gly Thr Met

355 360 365

Ser Ser Pro Leu Gln Cys Ile His Ser Pro Asp Leu

370 375 380

<210> 30

<211> 4124

<212> DNA

<213> Homo sapiens

<400> 30

atgagagaat gggttctgct catgtccgtg ctgctctgtg gcctggctgg cccacacac 60
ctgtccagc caagcctggt gctggacatg gccaaaggcc tcttgataa ctactgctc 120
ccggagaacc tgctgggcat gcaggaagcc atccagcagg ccatcaagag ccatgagatt 180
ctgagcatct cagacccgca gacgctggcc agtgtgctga cagccggggg gcagagctcc 240
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<211> 579

<212> DNA

<213> Homo sapiens

<400> 31

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<210> 32

<211> 633

<212> DNA

<213> Homo sapiens

<400> 32

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<210> 33

<211> 1047

<212> DNA

<213> Homo sapiens

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<210> 34

<211> 1706

<212> DNA

<213> Homo sapiens

<400> 34

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<211> 633

<212> DNA

<213> Homo sapiens

<400> 35

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<210> 36

<211> 1047

<212> DNA

<213> Homo sapiens

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<210> 37

<211> 1706

<212> DNA

<213> Homo sapiens

<400> 37

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<211> 1043

<212> DNA

<213> Homo sapiens

<400> 38

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<210> 39

<211> 1047

<212> DNA

<213> Homo sapiens

<400> 39

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<210> 40

<211> 1705

<212> DNA

<213> Homo sapiens

<400> 40

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<211> 1043

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<213> Homo sapiens

<400> 41

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<211> 4195

<212> DNA

<213> Homo sapiens

<400> 43

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<211> 425

<212> DNA

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<213> Homo sapiens

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<213> Homo sapiens

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<212> PRT

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Ile Glu Ser Val Leu Ser Ser Ser Gly Lys Arg Leu Gly

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<211> 18

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Phe Ser

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<210> 63

<211> 17

<212> PRT

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Glu Lys Met His Glu Gly Asp Glu Gly Pro Gly His His His Lys Pro

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Gly

<210> 64

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<212> PRT

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Asp Leu Gln Asn Phe Leu Lys Lys Glu Asn Lys Asn Glu

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<210> 65

<211> 19

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Val Lys Leu Gly His Pro Asp Thr Leu Asn Gln Gly Glu Phe Lys Glu

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15

Leu Val Arg

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48

<210> 67

<211> 48

<212> DNA

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<400> 67

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48

<210> 68

<211> 16

<212> PRT

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Phe Ser Trp Asp Asn Cys Phe Glu Gly Lys Asp Pro Ala Val Ile Arg

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<211> 585

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wsnacngcnw snggnytnyt nytntggcar ggngtngarg tnggngargc nggncarggn 180
aargayttya thwsnytnng nytnargay ggncayytng tnttymgnta ycarytnggn 240
wsnggngarg cnmgnytngt nwsngargay ccnathaayg ayggngartg gcaymgngtn 300
acngcnytnm gngarggnmg nmngngnwsn mgncargtng ayggngarga rytngtnwsn 360
ggnmgnwsnc cnggncnaa ygtngcngtn aaygcnaarg gnwsngnta yathggnggn 420
gcncngayg tngcnacnyt nacngnggn mgnttywsnw snggnathac nggntgygtn 480
aaraayytng tnytnayws ngcnmgncn ggngcncnc cncncarcc nytngayyt 540
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taygcnatgg cnaaraarga yccngarggn ytnttytnc argayaayat hgtngcngar 180
ttywsngtng aygaracngg ncaratgwsn gcncngcna arggnmgngt nmngnytnyt 240
aayaaytggg aygtntgygc ngayatggtn ggnacnttya cngayacnga rgayccngcn 300
aarttyaara tgaartaytg gggngtngcn wsnttytnc araarggnaa ygaygaycay 360
tggathgtng ayacngayta ygayacntay gcngtncart aywsntgymg nytnytnaay 420
ytngayggna cntgygcnga ywsntaywsn ttygtnttyw snmgngaycc naayggnytn 480
ccncngarg cncaraarat hgtngmncar mgncargarg aryntgyyt ngcnmgncar 540
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<400> 71
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garggnaarg ayccngcngt nathmgnwsn ytnacnytn arccngaycc nathgtngtn 180
ccnggnaayg tnacnytnws ngtngtnggn wsnacnwsng tnccnytnws nwsnccnytn 240
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gaytayathg gnwsntgyac nttygarca ytytgygayg tnytn gayat gytnathccn 360
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aargarggna cntaywsnyt nccnaarwsn garttygcng tnccngayyt ngarytnccn 480
wsntggytna cnacnggnaa ytaymgnath garwsngtny tnwsnwsnws nggnaarmgn 540
ytnggntgya thaarathgc ngcnwsnytn aarggnath 579

<210> 72
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<400> 72
Tyr Ser Leu Pro Lys Ser Glu Phe Ala Val Pro Asp Leu Glu Leu Pro
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<210> 73
<211> 193
<212> PRT
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<400> 73

Met Gln Ser Leu Met Gln Ala Pro Leu Leu Ile Ala Leu Gly Leu Leu

1 5 10 15

Leu Ala Thr Pro Ala Gln Ala His Leu Lys Lys Pro Ser Gln Leu Ser

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Ser Phe Ser Trp Asp Asn Cys Asp Glu Gly Lys Asp Pro Ala Val Ile

35 40 45

Arg Ser Leu Thr Leu Glu Pro Asp Pro Ile Val Val Pro Gly Asn Val

50 55 60

Thr Leu Ser Val Val Gly Ser Thr Ser Val Pro Leu Ser Ser Pro Leu

65 70 75 80

Lys Val Asp Leu Val Leu Glu Lys Glu Val Ala Gly Leu Trp Ile Lys

85 90 95

Ile Pro Cys Thr Asp Tyr Ile Gly Ser Cys Thr Phe Glu His Phe Cys

100 105 110

Asp Val Leu Asp Met Leu Ile Pro Thr Gly Glu Pro Cys Pro Glu Pro

115 120 125

Leu Arg Thr Tyr Gly Leu Pro Cys His Cys Pro Phe Lys Glu Gly Thr

130 135 140

Tyr Ser Leu Pro Lys Ser Glu Phe Val Val Pro Asp Leu Glu Leu Pro

145 150 155 160

Ser Trp Leu Thr Thr Gly Asn Tyr Arg Ile Glu Ser Val Leu Ser Ser

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Ile

<210> 74

<211> 83

<212> PRT

<213> Homo sapiens

<400> 74

Gly Asp Val Cys Gln Asp Cys Ile Gln Met Val Thr Asp Ile Gln Thr
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Ala Val Arg Thr Asn Ser Thr Phe Val Gln Ala Leu Val Glu His Val
20 25 30

Lys Glu Glu Cys Asp Arg Leu Gly Pro Gly Met Ala Asp Ile Cys Lys
35 40 45

Asn Tyr Ile Ser Gln Tyr Ser Glu Ile Ala Ile Gln Met Met Met His
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Met Gln Asp Gln Gln Pro Lys Glu Ile Cys Ala Leu Val Gly Phe Cys
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Asp Glu Val

<210> 75

<211> 115

<212> PRT

<213> Homo sapiens

<400> 75

Met Thr Cys Lys Met Ser Gln Leu Glu Arg Asn Ile Glu Thr Ile Ile

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Asn Thr Phe His Gln Tyr Ser Val Lys Leu Gly His Pro Asp Thr Leu
20 25 30

Asn Gln Gly Glu Phe Lys Glu Leu Val Arg Lys Asp Leu Gln Asn Phe
35 40 45

Leu Lys Lys Glu Asn Lys Asn Glu Lys Val Ile Glu His Ile Met Glu
50 55 60

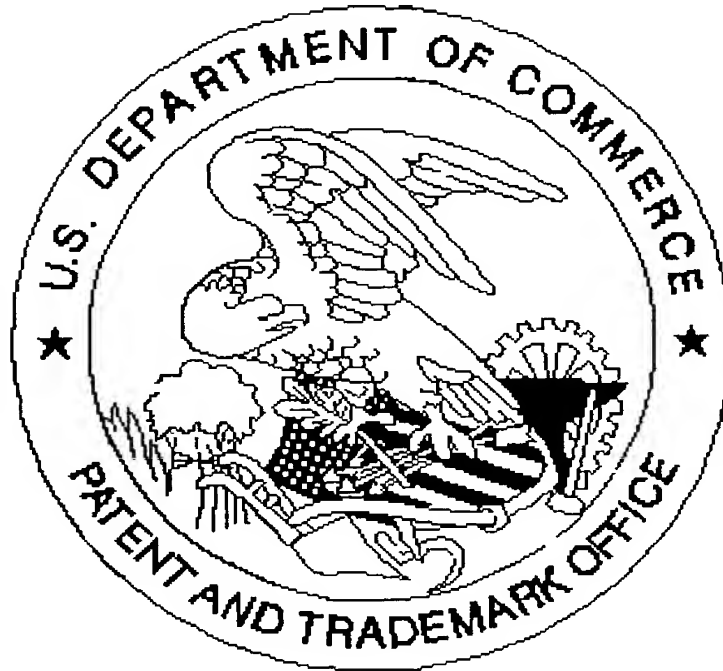
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85 90 95

Glu Gly Asp Glu Gly Pro Gly His His His Lys Pro Gly Leu Gly Glu
100 105 110

Gly Thr Pro
115

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